REMARKS

Favorable reconsideration of this application, in light of the preceding amendments and following remarks, is respectfully requested.

Claims 1-14 are pending in this application. Claims 1, 2, 8, 11 and 12 are amended and claims 15-20 have been cancelled. Claim 1 is the sole independent claim. Claims 7-10, 14, 17 and 18 have been withdrawn from consideration.

Applicants respectfully note that the present action does not indicate that the claim to foreign priority under 35 U.S.C. §119 has been acknowledged or that certified copies of all priority documents have been received by the U.S.P.T.O. Applicants respectfully request that the Examiner's next communication include an indication as to the claim to foreign priority under 35 U.S.C. §119 and an acknowledgement of receipt of the certified copies of all priority documents.

Applicants also respectfully note that the present action does not indicate that the drawings have been accepted by the Examiner. Applicants respectfully request that the Examiner's next communication include an indication as to the acceptability of the filed drawings or as to any perceived deficiencies so that the Applicants may have a full and fair opportunity to submit appropriate amendments and/or corrections to the drawings.

Restriction

In the Office Action, the Examiner states that in the light of the response to the restriction requirement, claims 7-10, 14, 17, 18 as filed on 7/17/2008 are withdrawn from consideration as being directed to non-elected invention. Applicants respectfully disagree.

In the Response to the Restriction Requirement filed on July 17, 2008, Applicants made a number of amendments to the original claims. As such, the

present claims 7-10 and 14 are different from original claims 7-10 and 14 to which the Restriction Requirement mailed June 17, 2008 was directed. In fact, all the claims 1-20 as filed on 7/17/2008 in response to the restriction requirement were directed towards a bioartificial implant according to Group I. Therefore, the amended claims 7-10, 14, 17, 18 as filed on 7/17/2008 relate to the invention of Group I.

For instance, claims 7-10 as filed on 7/17/2008 corresponded to the original claims 4-6, which were considered part of Group I by the examiner in the restriction requirement. Correspondingly, claim 14 as filed on 7/17/2008 relates to an insulin pump comprising the sugar detecting sensor element of claim 13, which is deemed to belong to the invention of Group I.

Applicants believe the Examiner withdrew these claims in error as the reference to withdrawn claims 7-10, 14, 17, and 18 refers to these claims as originally filed and not to claims 7-10, 14, 17, and 18 as filed on 7/17/2008. Further, claims 7-10 and 14 are dependent on claims 1 and 13, which are currently under examination, and are directed to the same class of invention.

Therefore, Applicants respectfully submit that claims 7-10 and 14 should be rejoined and examined in the present application.

Rejections under 35 U.S.C. § 112

Claims 1-6, 11-13, and 15-20 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection for the reasons detailed below.

Claims 15-20 have been cancelled, and therefore the rejection to claims 15-20 is now moot.

Applicants respectfully submit that claims 1 and 11-12 have been amended to overcome the outstanding 112 rejections. Further, as is well-known to one of ordinary skill in the art and is evident from the attached extract from Merriam-Webster's Collegiate Dictionary, "semipermeable" inherently defines partially but not freely or wholly permeable but instead permeable to some, usually small, molecules but not to other, usually larger, particles. A semipermeable membrane is a membrane that will allow molecules or ions to pass through it by diffusion or facilitated diffusion. The permeability of the membrane may depend on, for instance, the solute size, solubility, properties or chemistry.

Amended claim 1 also now states that the surface coating is permeable to "not interfere with the semipermeability of the semipermeable barrier". This feature is supported by the application as filed, e.g. on page 5, lines 4-7. Amended claim 2 corresponds to subject-matter of claims 1 and 2 as filed on 7/17/2008.

In addition, the expressions first side and second side have been consistently used instead of one side and other side. Furthermore, the expression "semipermeable barrier" has been consistently used throughout the claims instead of barrier.

The Applicants, therefore, respectfully request that the rejection to Claim 1-6, 11-13 and 15-20 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Khan

Claims 1-6, 11-13 and 15 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,387,327 to Khan. Applicants respectfully traverse this rejection for the reasons detailed below.

The Office Action stated that Khan teaches an implant comprising a semipermeable barrier coated with a bioactive metal such as titanium which allows or

prevents diffusion of substances, material and molecules to the opposite side of the barrier; that the substances are produced in a human or animal body, i.e., blood sugar; that Khan teaches the titanium to be deposited by spray deposition, i.e., an atomizing process; that the implant further comprises a sensor element enclosed by a membrane; that the sensor is disclosed as being a blood sugar detecting sensor element; and that thus, the reference anticipates the claimed subject matter.

The Examiner also states that Khan discloses titanium oxide deposited by spray deposition, and therefore, anticipates claim 1. Applicants respectfully disagree.

Khan does disclose that titanium oxide can be deposited by spray deposition. However, this titanium oxide is coated on a platinum or nickel wire to form a non-reactive semiconductor measurement electrode (column 3, lines 34-36; column 4, lines 29-35). Thus, the electrode wire in the sensor of Khan has a surface coating of titanium oxide and *not* the semipermeable membrane.

Furthermore, Khan discloses a bioartificial implant (non-enzymatic electrochemical sensor 10) comprising a semipermeable barrier (biocompatible membrane 15; column 3, lines 50-61). However, Khan does not disclose that the semipermeable barrier has any surface coating at all, and therefore, does not disclose a surface coating of a bioactive metal as recited in claim 1.

In addition, there is no guidance in Khan to one of ordinary skill in the art in applying the titanium oxide layer to the semipermeable membrane as the titanium oxide is used to achieve desired properties <u>in the electrode material</u>.

The Applicants, therefore, respectfully request that the rejection to Claim 1 under 35 U.S.C. § 102(b) be withdrawn.

Claim 15 has been cancelled. Therefore, the rejection to claim 15 is now moot. Claims 2-6 and 11-13, dependent on independent claim 1, are patentable for the reasons stated above with respect to claim 1 as well as for their own merits.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to independent claim 1 and all claims dependent thereon.

LaVan

Claims 1-5, 11 and 15 stand rejected under 35 U.S.C. § 102(b) as being Nature Biotech, Sept. 2003 by LaVan et al. ("LaVan"). Applicants respectfully traverse this rejection for the reasons detailed below.

The Office Action stated that LaVan teaches an implant comprising a semipermeable barrier coated with a bioactive metal such as titanium which allows or prevents diffusion of substances, material and molecules to the opposite side of the barrier; that the substances are produced in a human or animal body, i.e., cells, insulin, interferon; and that, thus, the reference anticipates the claimed subject matter. Applicants respectfully disagree.

LaVan discloses a bioartificial implant (titanium tube implant, Fig. 3) comprising a semipermeable barrier (semi-permeable membrane, Fig. 3). However, LaVan does not disclose that the semipermeable barrier is coated with a bioactive metal as is recited in claim 1. In clear contrast, LaVan instead discloses that the tube of the implant can be made of titanium (page 1186, section Chambers). There is no indication in LaVan that the semipermeable membrane of the implant should have any coating.

The attached document relating to Viadur® is the product description of the leuprolide acetate implant mentioned in LaVan and disclosed in Fig. 3. As is evident from the section "Description" of that document, the semi-permeable membrane is a polyurethane rate-controlling membrane. However, no indication of any surface coating on the membrane is given in the Viadur® document or in LaVan.

Further, no disclosure in LaVan would guide one of ordinary skill in the art towards the idea of applying a surface coating of a bioactive metal on the semi-permeable membrane of the implant.

The Applicants, therefore, respectfully request that the rejection to Claim 1 under 35 U.S.C. § 102(b) be withdrawn.

Claim 15 has been cancelled. Therefore, the rejection to claim 15 is now moot. Claims 2-5 and 11, dependent on independent claim 1, are patentable for the reasons stated above with respect to claim 1 as well as for their own merits.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to independent claim 1 and all claims dependent thereon.

Peery

Claim 1-5 and 15 stand rejected under 35 U.S.C. § 102(a) as being anticipated by U.S. Publication No. 2003/0108590 to Peery et al. ("Peery"). Applicants respectfully traverse this rejection for the reasons detailed below.

The Office Action stated that Peery teaches an implant comprising a semipermeable barrier coated with a bioactive metal such as titanium which allows or prevents diffusion of substances, material and molecules to the opposite side of the barrier; that the substances are produced in a human or animal body, i.e., insulin; and that thus, the reference anticipates the claimed subject matter. Applicants respectfully disagree.

Peery discloses a bioartifical implant (osmotic delivery system 10) comprising a semipermeable barrier (membrane material 30; paragraphs 41, 42). Peery discloses that the capsule in which the membrane material is attached can be made of a biocompatible metal, such as titanium (paragraph 44). The membrane material is made of a polymeric material as mentioned in paragraph 46.

However, Peery does not disclose that the membrane material has a surface coating of a bioactive material. In clear contrast, Peery is totally silent regarding any surface coating applied to the membrane material. There is therefore no indication in Peery that would guide one of ordinary skill in the art towards applying any such surface coating to the membrane material.

The Applicants, therefore, respectfully request that the rejection to Claim 1 under 35 U.S.C. § 102(a) be withdrawn.

Claim 15 has been cancelled. Therefore, the rejection to claim 15 is now moot. Claims 2-5, dependent on independent claim 1, are patentable for the reasons stated above with respect to claim 1 as well as for their own merits.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to independent claim 1 and all claims dependent thereon.

Brauker

Claims 1-3, 11-13 and 15 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,782,912 to Brauker et al. ("Brauker"). Applicants respectfully traverse this rejection for the reasons detailed below.

The Office Action stated that Brauker teaches an implant comprising a semipermeable barrier which allows or prevents diffusion of substances, material and molecules to the opposite side of the barrier; that the substances are produced in a human or animal body, i.e., blood sugar; that the implant further comprises a sensor element enclosed by a membrane; that the sensor is disclosed as being a blood sugar detecting sensor element; and that, thus, the reference anticipates the claimed subject matter. Applicants respectfully disagree.

Brauker discloses a bioartificial implant (sensor 80) comprising a semipermeable barrier (second membrane 50; column 3, lines 64-66; column 4, lines

8-12; column 13, lines 24-33). Brauker further discloses that a first membrane (membrane 42) surrounds the second membrane (column 3, lines 62-63; column 13, lines 8-10). This first membrane is a porous polymer membrane having a specific average nominal pore size and average strand size to induce close vascularisation (column 3, lines 62-63; column 4, lines 50-56; column 7, lines 40-43).

Brauker continues by speculating that the disclosed effects are believed to be achieved by a variety of polymers and biocompatible ceramics and metals (column 14, lines 6-21). Thus, Brauker speculates that biocompatible metals, if they can be manipulated to provide the three dimensional structures of the asymmetrical membrane structure, could substitute the polymers as membrane material.

However, Brauker does not disclose that a semi-permeable barrier has a surface coating of a bioactive metal. In clear contrast, Brauker at most speculates that a biocompatible metal can be used as semipermeable membrane. Thus, there is no indication in Brauker that guides one of ordinary skill in the art towards applying a surface coating of a bioactive metal to a semipermeable barrier. On the contrary, Brauker guides one of ordinary skill in the art towards usage of a sandwich membrane structure, which is a fundamentally different approach than that recited in claim 1.

The Applicants, therefore, respectfully request that the rejection to Claim 1 under 35 U.S.C. § 102(b) be withdrawn.

Claim 15 has been cancelled. Therefore, the rejection to claim 15 is now moot. Claims 2-3 and 11-13, dependent on independent claim 1, are patentable for the reasons stated above with respect to claim 1 as well as for their own merits.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to independent claim 1 and all claims dependent thereon.

Antananvich

Claims 1-3, 11 and 15 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,372,244 to Antananvich et al. ("Antananvich"). Applicants respectfully traverse this rejection for the reasons detailed below.

The Office Action stated that Antananvich teaches an implant comprising a semipermeable barrier coated with a bioactive metal, i.e., barium and calcium which allows or prevents diffusion of substances, material and molecules to the opposite side of the barrier; that the substances are produced in a human or animal body, i.e., cells; and that, thus, the reference anticipates the claimed subject matter. Applicants respectfully disagree.

Antanavich discloses a bioartificial implant (thin sheet bioartificial implant, Fig. 1) comprising a semipermeable barrier (coat 4; column 19, lines 10-20, 54-56; column 20, lines 55-61; column 21, lines 27-28). Antanavich also discloses that the semipermeable coat can be covered by an alginate overcoat to enhance the biocompatibility of the implant (column 19, lines 56-58; column 21, lines 27-28).

However, Antanavich does not disclose that the semipermeable barrier has a surface coating of a bioactive metal as recited in claim 1. In clear contrast, the alginate coat of Antanavich has a further alginate overcoat.

The Examiner refers to column 20, lines 30-35 which merely states that the multivalent cation is mixed with the alginate in order to form a non-dissolvable gel made of calcium, barium or zinc ions. Therefore, Antanavich does not disclose a surface coating with any bioactive metal, but merely inclusion of multivalent ions in the alginate material to form crosslinks between the individual alginate strands and an alginate gel. This is well-known in the art, such as illustrated in pages 8 and 9 of the provided document Alginates from FMC BioPolymer.

The Applicants, therefore, respectfully request that the rejection to Claim 1 under 35 U.S.C. § 102(b) be withdrawn.

Claim 15 has been cancelled. Therefore, the rejection to claim 15 is now moot. Claims 2-3 and 11, dependent on independent claim 1, are patentable for the reasons stated above with respect to claim 1 as well as for their own merits.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to independent claim 1 and all claims dependent thereon.

CONCLUSION

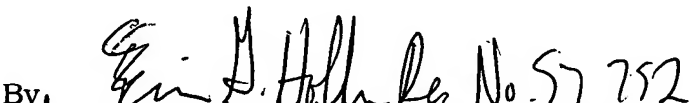
In view of the above remarks and amendments, the Applicants respectfully submit that each of the pending objections and rejections has been addressed and overcome, placing the present application in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to contact the undersigned.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Erin G. Hoffman, Reg. No. 57,752, at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 08-0750 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

HARNESS, DICKEY, & PIERCE, P.L.C.

By  Reg. No. 57,752
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DJD/EGH:ljs

Enclosures: Definition of "semipermeable" – Webster's Collegiate Dictionary
Viadur® Description – Bayer Pharmaceuticals
FMC Biopolymer – "Alginates – A World of Possibilities Lies Just Below the Surface"

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mē-'fī-nisht, ˌse-ˌmī-, -mi-\ *adj* (1902) : partially finished, *esp, of steel* : rolled from raw ingots into shapes (as billets) suitable for further processing

s\ *adj* (ca. 1950) : conforming somewhat to the lines

\ *adj* (1925) 1 : somewhat flexible 2 *of a book* : having a thin board stiffener under the covering material

d\ *adj* (ca. 1735) : having the qualities of both a fluid and a solid

ous (fluid and ~ lubricants) — semifluid *n*

or-mal\ *adj* (1906) : being or suitable for an occasion between formal and informal ⟨a ~ dinner⟩ ⟨~ gowns⟩

mality ⟨a ~ dinner⟩ ⟨~ gowns⟩

mē-glās, 'se-ˌmī-, -mi-, -ˌglȯs\ *adj* (1937) : having a low degree of gloss

producing a finish midway between glossy and flat

mē-ˌgrüp, 'se-ˌmī-, -mi-\ *n* (1904) : a mathematical set under an associative binary operation

dent \-in-də-'pen-dənt\ *adj* (1860) : partially independent

AUTONOMOUS

\-'ē-jən-ˌder-ē\ *adj* (1878) : having historical foundation in legend

thal\ *n* (1919) : a mutation that in the homozygous state causes more than 50 percent mortality but not complete

lethal *adj*

kwəd\ *adj* (1684) : having the qualities of both a liquid and a solid

LIQUID ⟨~ manure⟩ — semiliquid *n*

-lē-rət *also* -'li-trət\ *adj* (1927) 1 a : able to read and write elementary level b : able to read but unable to write 2 : having knowledge or understanding : not well-versed — semi-

ˌlāg\ *adj* (1921) : SEMILOGARITHMIC

\-ˌlō-gə-'rith-mik, -ˌlä-\ *adj* (1919) : having one scale logarithmic and the other arithmetic — used of graph paper or of

paper

-nər\ *adj* [NL *semilunaris*, fr. L *semi-* + *lunaris* lunar] : shaped like a crescent

n (ca. 1719) : any of the crescent-shaped cusps that occur in pairs, three between the heart and the aorta and another of three between the heart and the pulmonary artery, are forced apart by the ventricles during systole and pushed together by pressure in the arteries during diastole, and prevent regurgitation of blood from the ventricles; *also* : either set of three cusps

\-'lüs-trəs\ *adj* (1953) : slightly lustrous

axis \-'mā-jər\ *n* (1899) : one half of the major axis of an ellipse formed by the orbit of a planet)

also **semi-mat** *or* **semi-matt** \-'mat\ *adj* [*semi-* + *²matte*] : having a slight luster

\-'me-t²l\ *n* (1661) : an element (as arsenic) possessing metallic properties in an inferior degree and not malleable — **semi-metallic** \-mə-'na-lik\ *adj*

\-'mī-(ˌ)krō\ *adj* (1935) : of, relating to, or dealing with an intermediate between those treated as micro and macro ⟨~ chlorine⟩ ⟨a ~ balance⟩

axis \-'mī-nər-\ *n* (1909) : one half of the minor axis of an ellipse (as that formed by the orbit of a planet)

\-'mȯist\ *adj* (1903) : slightly moist

-tic \-mə-'nas-tik\ *adj* (1911) : having some features characteristic of a monastic order

th-ly \-'mən(t)th-lē\ *n* (1851) : a semimonthly publication

hly *adj* (1860) : occurring twice a month

hly *adv* (ca. 1890) : twice a month

-cal \-'mis-ti-kəl\ *adj* (1890) : having some of the qualities of mysticism

\'se-mə-nᵊl\ *adj* [ME, fr. MF, fr. L *seminalis*, fr. *semin-, semen* seed — more at SEMEN] (14c) 1 : of, relating to, or consisting of seed 2 : containing or contributing the seeds of later development : CREATIVE, ORIGINAL ⟨a ~ book⟩ ⟨one of the most ~ of the writers⟩ — **sem·i·nal·ly** \-nᵊl-ē\ *adv*

duct *n* (ca. 1909) : a tube or passage serving esp. or exclusively to convey sperm duct of the testis and in the human male being made up of the coils of the epididymis, the vas deferens, and the ejaculatory duct

fluid *n* (ca. 1929) 1 : SEMEN 2 : the part of the semen that is furnished by various accessory glands : semen excepting the spermatozoa

vesicle *n* (ca. 1890) : either of a pair of glandular pouches that open on either side of the male reproductive tract and in the human secrete a sugar- and protein-containing fluid into the ejaculatory

\'se-mə-ˌnär\ *n* [G, fr. L *seminarium* nursery] (1889) 1 : a group of advanced students studying under a professor with each doing original research and all exchanging results through reports and discussion 2 a (1) : a course of study pursued by a seminar (2) : an advanced or graduate course often featuring informality and discussion b : a scheduled meeting of a seminar or a room for such meetings 3 : a conference for giving and discussing information

ar·i·an \ˌse-mə-'ner-ē-ən\ *n* (1794) : a student in a seminary esp. of the Roman Catholic Church

a·rist \'se-mə-nə-rist\ *n* (1835) : SEMINARIAN

ary \'se-mə-ˌner-ē\ *n, pl* **-nar·ies** [ME, seedbed, nursery, fr. L *seminarium*, fr. *semin-, semen* seed] (1542) 1 : an environment in which something originates and from which it is propagated ⟨a ~ of crime⟩ 2 a : an institution of secondary or higher education b : institution for the training of candidates for the priesthood, ministry, or rabbinate

a·ra·ral \ˌse-mē-'na-chə-rəl, ˌse-ˌmī-, -mi-, -'nach-rəl\ *adj* (ca. 1880) : modified by human influence but retaining many natural features ⟨a ~ park⟩

-fer·ous \ˌse-mə-'ni-f(ə-)rəs\ *adj* [L *semin-, semen* seed + E -*ferous*] (1692) : producing or bearing seed or semen

-ferous tubule *n* (1860) : any of the coiled threadlike tubules that make up the bulk of the testis and are lined with a layer of epithelial tissue from which the spermatozoa are produced

Sem·i·nole \'se-mə-ˌnōl\ *n, pl* **Seminoles** *or* **Seminole** [Creek *simanó·li* fugitive, wild, alter. of *simalò·ni*, fr. AmerSp *cimarrón* wild] (1771) : a member of any of the groups of American Indians that emigrated to Florida from Georgia and Alabama in the 18th century and that are now located in southern Florida and Oklahoma

semi·no·mad \ˌse-mē-'nō-ˌmad, ˌse-ˌmī-, -mi-\ *n* (ca. 1934) : a member of a people living usu. in portable or temporary dwellings and practicing seasonal migration but having a base camp at which some crops are cultivated — **semi·no·mad·ic** \-nō-'ma-dik\ *adj*

semi·nude \-'nüd, -'nyüd\ *adj* (1849) : partially nude — **semi·nu·di·ty** \-'nü-də-tē, -'nyü-\ *n*

semi·of·fi·cial \-ə-'fi-shəl\ *adj* (1806) : having some official authority or standing — **semi·of·fi·cial·ly** \-'fi-sh(ə-)lē\ *adv*

se·mi·ol·o·gy \ˌsē-mē-'ä-lə-jē, ˌse-mē-, ˌsē-ˌmī-\ *n* [Gk *sēmeion* sign] (ca. 1890) : the study of signs; *esp* : SEMIOTIC — **se·mi·o·log·i·cal** \(ˌ)sē-ˌmī-ə-'lä-ji-kəl, ˌse-mē-ə-\ *adj* — **se·mi·o·log·i·cal·ly** \-ə-'lä-ji-k(ə-)lē\ *adv* — **se·mi·ol·o·gist** \-'ä-lə-jist\ *n*

semi·opaque \ˌse-mē-ō-'pāk, ˌse-ˌmī-, -mi-\ *adj* (1691) : nearly opaque

se·mi·o·sis \ˌsē-mē-'ō-səs, ˌse-mē-, ˌsē-ˌmī-\ *n* [NL, fr. Gk *sēmeiōsis* observation of signs, fr. *sēmeioun* to observe signs, fr. *sēmeion*] (ca. 1907) : a process in which something functions as a sign to an organism

se·mi·ot·ic \-'ä-tik\ *or* **se·mi·ot·ics** \-tiks\ *n, pl* **semiotics** [Gk *sēmeiōtikos* observant of signs, fr. *sēmeioustai* to interpret signs, fr. *sēmeion* sign, fr. *sēma* sign] (1880) : a general philosophical theory of signs and symbols that deals esp. with their function in both artificially constructed and natural languages and comprises syntactics, semantics, and pragmatics — **semiotic** *adj* — **se·mi·o·ti·cian** \-ə-'ti-shən\ *n* — **se·mi·ot·i·cist** \-'ä-tə-sist\ *n*

semi·pal·mat·ed \ˌse-mē-'pal-ˌmā-təd, ˌse-ˌmī-, -mi-, -'pāl-, -'pā-\ *adj* (1785) : having the toes joined only part way down with a web ⟨a plover with ~ feet⟩

semi·par·a·sit·ic \-ˌpar-ə-'si-tik\ *adj* (ca. 1880) : of, relating to, or being a parasitic plant that contains some chlorophyll and is capable of photosynthesis — **semi·par·a·site** \-'par-ə-ˌsīt\ *n*

semi·per·ma·nent \-'pər-mə-nənt, -'pərm-nənt\ *adj* (ca. 1890) : lasting or intended to last for a long time but not permanent

semi·per·me·able \-'pər-mē-ə-bəl\ *adj* (1888) : partially but not freely or wholly permeable; *specif* : permeable to some usu. small molecules but not to other usu. larger particles ⟨a ~ membrane⟩ — **semi·per·me·abil·i·ty** \-ˌpər-mē-ə-'bi-lə-tē\ *n*

semi·po·lit·i·cal \-pə-'li-ti-kəl\ *adj* (1857) : of, relating to, or involving some political features or activity

semi·pop·u·lar \-'pä-pyə-lər\ *adj* (1860) : somewhat popular

semi·por·ce·lain \-'pȯr-s(ə-)lən, -'pȯr-\ *n* (1880) : any of several ceramic wares resembling or imitative of porcelain; *esp* : a relatively high-fired and hard-glazed white earthenware widely used for tableware

semi·por·no·graph·ic \-ˌpȯr-nə-'gra-fik\ *adj* (1964) : somewhat pornographic — **semi·por·nog·ra·phy** \-pȯr-'nä-grə-fē\ *n*

semi·post·al \-'pōs-t²l\ *n* (1927) : a postage stamp sold at a premium over its postal value esp. for a humanitarian purpose

semi·pre·cious \-'pre-shəs\ *adj* (ca. 1890) *of a gemstone* : of less commercial value than a precious stone

semi·pri·vate \-'prī-vət\ *adj* (1876) : of, receiving, or associated with hospital service giving a patient more privileges than a ward patient but fewer than a private patient

semi·pro \'se-mē-ˌprō, 'se-ˌmī-, -mi-\ *adj or n* (1908) : SEMIPROFESSIONAL

¹semi·pro·fes·sion·al \ˌse-mē-prə-'fesh-nəl, ˌse-ˌmī-, -mi-, -'fe-shə-nᵊl\ *n* (1889) : one who engages in an activity (as a sport) semiprofessionally

²semiprofessional *adj* (1900) 1 : engaging in an activity for pay or gain but not as a full-time occupation 2 : engaged in by semiprofessional players ⟨~ baseball⟩ — **semi·pro·fes·sion·al·ly** *adv*

semi·pub·lic \-'pə-blik\ *adj* (1804) 1 : open to some persons outside the regular constituency 2 : having some features of a public institution; *specif* : maintained as a public service by a private nonprofit organization

semi·quan·ti·ta·tive \-'kwän-tə-ˌtā-tiv\ *adj* (1927) : constituting or involving less than quantitative precision — **semi·quan·ti·ta·tive·ly** *adv*

semi·qua·ver \'se-mē-ˌkwā-vər, 'se-ˌmī-, -mi-\ *n* (1576) : SIXTEENTH NOTE

semi·re·li·gious \ˌse-mē-ri-'li-jəs, ˌse-ˌmī-, -mi-\ *adj* (1864) : somewhat religious

semi·re·tired \-ri-'tīrd\ *adj* (1937) : working only part-time esp. because of age or ill health

semi·re·tire·ment \-'tīr-mənt\ *n* (1923) : the state or condition of being semiretired

semi·rig·id \-'ri-jəd\ *adj* (1908) 1 : rigid to some degree or in some parts 2 *of an airship* : having a flexible cylindrical gas container with an attached stiffening keel that carries the load

semi·rur·al \-'růr-əl\ *adj* (1835) : somewhat rural

semi·sa·cred \-'sā-krəd\ *adj* (1898) : SEMIRELIGIOUS

semi·se·cret \-'sē-krət\ *adj* (ca. 1903) : moderately soft; *specif* : firm but easily cut ⟨~ cheese⟩

semi·sol·id \-'sä-ləd\ *adj* (1834) : having the qualities of both a solid and a liquid : highly viscous — **semisolid** *n*

semi·sub·mers·ible \-səb-'mər-sə-bəl\ *adj* (1962) : being a floating deepwater drilling platform that is towed to a desired location and then partially flooded for stabilization and usu. anchored — **semisubmersible** *n*

Viadur®
(leuprolide acetate implant)

08840302, R.2 11/05

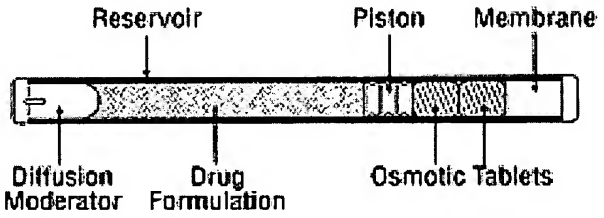
DESCRIPTION

Viadur® (leuprolide acetate implant) is a sterile nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate (Figure A). Viadur® incorporates DUROS® technology. The system contains 65 mg of leuprolide (free base). Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The implant is inserted subcutaneously in the inner aspect of the upper arm. After 12 months, the implant must be removed. At the time an implant is removed, another implant may be inserted to continue therapy.

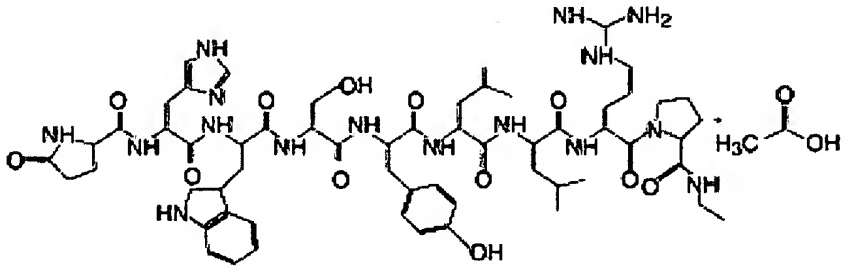
Viadur® contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide free base) dissolved in 104 mg dimethyl sulfoxide. The 4 mm by 45 mm titanium alloy reservoir houses a polyurethane rate-controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator. The reservoir also contains the osmotic tablets, which are not released with the drug formulation. The osmotic tablets are composed of sodium chloride, sodium carboxymethyl cellulose, povidone, magnesium stearate, and sterile water for injection. Polyethylene glycol fills the space between the osmotic tablets and the reservoir. A minute amount of silicone medical fluid is used during manufacture as a lubricant. The weight of the implant is approximately 1.1g.

Figure A.

Viadur® (leuprolide acetate implant) (diagram not to scale)



The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt), with the following structural formula:



CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that after an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in concentrations of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur within 2 to 4 weeks after initiation of treatment.

One Viadur® Implant nominally delivers 120 micrograms of leuprolide acetate per day over 12 months. Leuprolide acetate is not active when given orally.

PHARMACOKINETICS

Absorption

After insertion of Viadur®, mean serum leuprolide concentrations were 16.9 ng/mL at 4 hours and 2.4 ng/mL at 24 hours. Thereafter, leuprolide was released at a constant rate. Mean serum leuprolide concentrations were maintained at 0.9 ng/mL (0.3 to 3.1 ng/mL; SD = ±0.4) for 12 months. Upon removal and insertion of a new Viadur® at 12 months, steady-state serum leuprolide concentrations were maintained.

Distribution

The mean steady-state volume of distribution of leuprolide following 1 mg intravenous (IV) bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.[1]

Metabolism

In healthy male volunteers administered a 1 mg IV bolus of leuprolide, the mean systemic clearance was 8.34 L/h, with a terminal elimination half-life of approximately 3 hours, based on a two-compartment model.[1]

A pentapeptide (M-1) is the major leuprolide metabolite upon administration with different leuprolide acetate formulations. No drug metabolism study was conducted with Viadur®.

Excretion

No drug excretion study was conducted with Viadur®.

Dose Proportionality

In a study comparing one Viadur® implant to two Viadur® implants, mean serum leuprolide concentrations were proportional to dose.

Special Populations

Geriatrics

The majority (88%) of the 131 patients studied in clinical trials were age 65 and over.

Pediatrics

The safety and effectiveness of Viadur® in pediatric patients have not been established (see **CONTRAINDICATIONS**).

Race

In the patients studied (80 Caucasian, 23 Black, 3 Hispanic), mean serum leuprolide concentrations were similar.

Renal and Hepatic Insufficiency

The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

Drug-Drug Interactions

No pharmacokinetic drug-drug interaction studies were conducted with Viadur®.

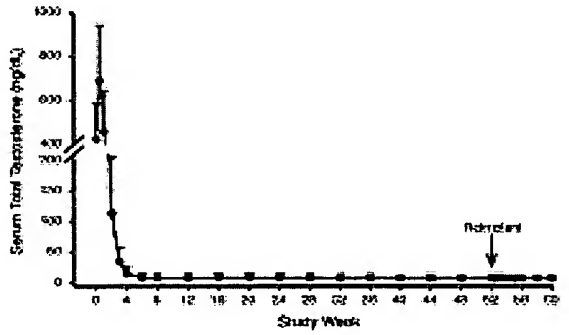
CLINICAL STUDIES

In two open-label, non-comparative, multicenter studies, 131 patients with prostatic cancer were treated with Viadur® and evaluated for up to two years. Two-thirds of the patients had stage C or less advanced disease. The dose-ranging study assessed serum testosterone as the primary efficacy endpoint in 51 patients treated with either one [n=27] or two [n=24] implants for 12 months. The confirmatory study evaluated achievement and maintenance of serum testosterone suppression in 80 patients each treated with one implant for 12 months. Both studies included a removal procedure and insertion of a new implant with evaluation for 12 additional months.

Following the initial insertion in patients receiving one implant, mean serum testosterone concentrations increased from 422 ng/dL at baseline to 690 ng/dL on Day 3, then decreased to below baseline by week two (Figure B). Serum testosterone decreased below the 50 ng/dL castrate threshold by week four in all but one patient [106 of 107 patients, 99%]. Once serum testosterone suppression was achieved [one patient was not continuously suppressed until week 28], testosterone remained suppressed below the castrate threshold for the duration of the treatment phase.

Figure B.

Mean (+SD) Serum Total Testosterone Concentrations – All Patients (n=107) Who Received One Implant



(Diagonal lines [//] indicate change in axis scale)

Most patients [n=118] had a new implant inserted for a second year of therapy following removal of the first implant(s). No patient experienced a clinically significant increase in serum testosterone [acute-on-chronic phenomenon] upon removal of the original implant(s) and insertion of a new implant. Suppression of serum testosterone was maintained in all patients through the two-month follow-up period following removal of the first implant(s) and insertion of a new implant.

Serum Prostate Specific Antigen (PSA) was monitored as a secondary endpoint in the clinical studies with Viadur®. Serum PSA decreased in all patients after they began treatment with Viadur®. At six months, PSA concentrations decreased from baseline by at least 90% in 74.2% of the 97 evaluable patients.

Periodic monitoring of serum testosterone and PSA concentrations is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved.

INDICATIONS AND USAGE

Viadur® is indicated in the palliative treatment of advanced prostate cancer.

CONTRAINDICATIONS

1. Viadur® is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs, or any of the components in Viadur®. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.[2]
2. Viadur® is contraindicated in women and in pediatric patients and was not studied in women or children. Moreover, leuprolide acetate can cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

WARNINGS

Viadur®, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction (see **PRECAUTIONS**).

Cases of ureteral obstruction and spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LH-RH agonists.

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

PRECAUTIONS

General

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS**).

X-rays do not affect Viadur® functionality. Viadur® is radio-opaque and is well visualized on X-rays.

The titanium alloy reservoir of Viadur® is nonferromagnetic and is not affected by magnetic resonance imaging (MRI). Slight image distortion around Viadur® may occur during MRI procedures.

Information for Patients

An information leaflet for patients is included with the product.

Laboratory tests

Response to Viadur® should be monitored by measuring serum concentrations of testosterone and prostate-specific antigen periodically.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Drug Interactions

See **PHARMACOKINETICS.**

Drug/Laboratory Test Interactions

Therapy with leuprolide results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprolide therapy may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. In rats, dose-related increases of benign pituitary hyperplasia and benign pituitary adenomas were noted at 24 months when the drug was administered subcutaneously at high daily doses (4 to 24 mg/m^2, 50 to 300 times the daily human exposure based on body surface area). There were significant but not dose-related increases of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at up to 180 mg/m^2 (over 2000 times the daily human exposure based on body surface area) for 2 years.

Mutagenicity studies were performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Pregnancy, Teratogenic Effects

Pregnancy Category X (see **CONTRAINDICATIONS**).

Pediatric Use

Viadur® is contraindicated in pediatric patients and was not studied in children (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The safety of Viadur® was evaluated in 131 patients with prostate cancer treated for up to 24 months in two clinical trials. Viadur®, like other LHRH analogs, caused a transient increase in serum testosterone concentrations during the first 2 weeks of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see **WARNINGS** and **PRECAUTIONS**).

In the above-described clinical trials, the transient increase in serum testosterone concentrations was associated with an exacerbation of disease symptoms, manifested by pain or bladder outlet obstructive symptoms (urinary retention or frequency) in 6 (4.6%) patients.

The majority of local reactions associated with initial insertion or removal and insertion of a new implant began and resolved within the first two weeks. Reactions persisted in 9.3% of patients. 10.3% of patients developed application-site reactions after the first two weeks following insertion.

Local reactions after initial insertion of a single implant included bruising (34.6%) and burning (5.6%). Other, less frequently reported, reactions included pulling, pressure, itching, erythema, pain, edema, and bleeding.

In these two clinical trials, four patients had local infection/inflammations that resolved after treatment with oral antibiotics.

Local reactions following insertion of a subsequent implant were comparable to those seen after initial insertion.

In the first 12 months after initial insertion of the implant(s), an implant extruded through the incision site in three of 131 patients (see **INSERTION AND REMOVAL PROCEDURES** for correct implant placement).

The following possibly or probably related systemic adverse events occurred during clinical trials within 24 months of treatment with Viadur®, and were reported in ≥2% of patients (Table 1).

Table 1

Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥ 2% of Patients Treated with Viadur® for up to 24 months

Body System	Adverse Event	Number (%)
Body as a Whole	Asthenia	10 (7.6%)
	Headache	6 (4.6%)
	Extremity pain	4 (3.1%)
Cardiovascular	Vasodilatation (hot flashes)*	89 (67.9%)
Digestive	Diarrhea	3 (2.3%)
Hematology and Lymphatic	Ecchymosis	6 (4.6%)
	Anemia	3 (2.3%)
Metabolic and Nutritional	Peripheral edema	4 (3.1%)
	Weight gain	3 (2.3%)
Nervous	Depression	7 (5.3%)
Respiratory	Dyspnea	3 (2.3%)
Skin	Sweating*	7 (5.3%)
	Alopecia	3 (2.3%)
Urogenital	Gynecomastia/breast enlargement*	9 (6.9%)
	Nocturia	5 (3.8%)
	Urinary frequency	5 (3.8%)
	Testis atrophy or pain*	5 (3.8%)
	Breast pain*	4 (3.1%)
	Impotence*	3 (2.3%)

* Expected pharmacologic consequences of testosterone suppression.

In addition, the following possibly or probably related systemic adverse events were reported by <2% of patients using Viadur® in clinical studies.

General: General pain, chills, abdominal pain, malaise, dry mucous membranes

Gastrointestinal: Constipation, nausea

Hematologic: Iron deficiency anemia

Metabolic: Edema, weight loss

Musculoskeletal: Bone pain, arthritis

Nervous: Dizziness, insomnia, paresthesia, amnesia, anxiety

Skin: Pruritus, rash, hirsutism

Urogenital: Urinary urgency, prostatic disorder, urinary tract infection, dysuria, urinary incontinence, urinary retention

Changes in Bone Density

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least 6 months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Postmarketing

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, opthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Ninety-seven of the 131 patients in the two-year duration studies that supported approval of Viadur® continued in an open-label, third-year extension study. One patient prematurely withdrew due to lack of efficacy that was attributed to a defective implant. Fifty of these patients continued in an open-label, fourth-year extension study. No spontaneous implant extrusions were reported in these extension studies. Since Viadur® has been commercially available, <1% of patients implanted have been reported to have a spontaneous implant extrusion (with or without associated infection).

Additional adverse events have been reported from US post-marketing experience with Viadur®. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been reported infrequently and include fatigue, hypertension, migration of implant, syncope, tremor, and vomiting.

OVERDOSAGE

In clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to 2 years caused no adverse effects differing from those observed with the 1 mg/day dose. The adverse event profiles were similar in patients receiving one or two Viadur® implants.

DOSAGE AND ADMINISTRATION

The recommended dose of Viadur® is one implant for 12 months. Each implant contains 65 mg leuprolide. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of leuprolide for 12 months of hormonal therapy.

Viadur® must be removed after 12 months of therapy. At the time an implant is removed, another implant may be inserted to continue therapy. (See **INSERTION AND REMOVAL PROCEDURES**.)

INSERTION AND REMOVAL PROCEDURES

Viadur® is supplied in a box containing one sterile Viadur® implant in a sealed vial, one Viadur® sterile implanter, one sealed container of lidocaine HCl USP 2%, 10 mL, and one sterile Viadur® Kit. The Viadur® Kit is designed to provide a sterile field and supplies to facilitate the insertion and/or subsequent removal of the implant.

In addition to the Viadur® Kit, sterile gloves are required for the insertion procedure and subsequent removal of the implant.

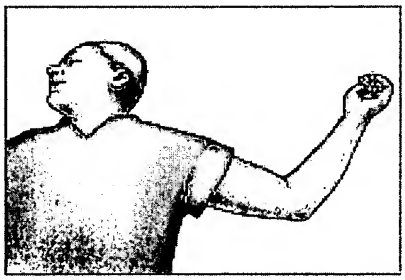
INSERTION PROCEDURE

Under aseptic conditions, an implanter is used to place the implant under the skin.

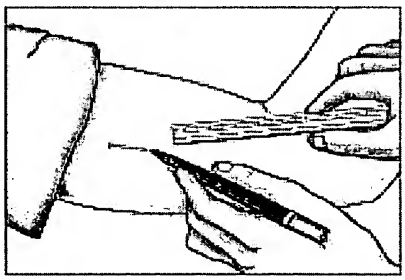
The implant is inserted using the procedure outlined below.

Identifying the Insertion Site

1. Have the patient lie on his back on the examination table, with his left arm (if the patient is left-handed, the right arm) flexed at the elbow and externally rotated so that his hand is out to his side.

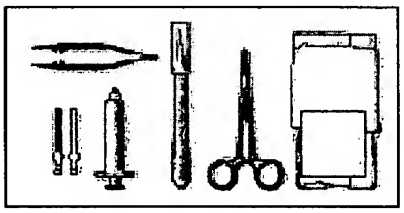


Using a pen and ruler, mark a site on the inner, upper arm approximately 8-10 cm above the elbow crease in the groove between the biceps and triceps muscles. Make sure that the site is unaffected by movement of the muscles.



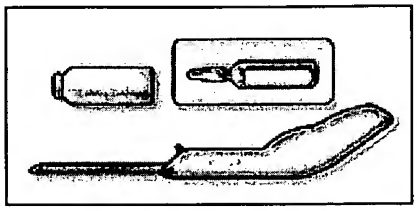
Preparing the Sterile Field

1. To establish a sterile field, carefully open the sterile Viadur® Kit. The sterile kit contains:
   - 1 scalpel
   - 1 forceps
   - 1 syringe
   - 1 package povidone-iodine swabs
   - 1 package wound closure strips
   - 1-22 Ga x 1.5" needle
   - 1-25 Ga x 1.5" needle
   - 6 gauze sponges
   - 2 alcohol prep swabs
   - 1 package skin protectant
   - 1 bandage
   - 1 fenestrated drape
   - 1 marking pen
   - 1 ruler

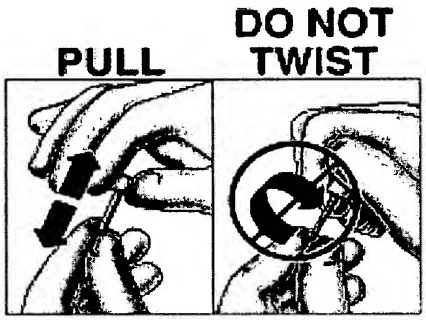


1 mosquito clamp

2. The implant tray contains:
   1 sealed vial, which contains the Viadur® implant
   1 sterile implanter
   1 sealed container of lidocaine HCl USP 2%, 10 mL



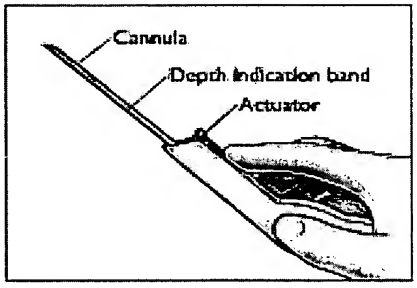
To open the vial, remove the metal band from the bottle and pull up the stopper. Carefully drop the implant from the bottle onto the sterile field. Then, carefully drop the implanter and the container of lidocaine onto the sterile field.



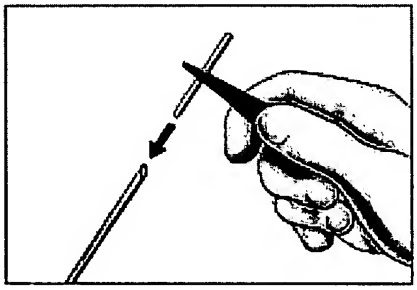
Using sterile technique, remove the protective cap from the implant by pulling the cap straight off. **DO NOT TWIST CAP OFF AS IT MAY UNSCREW THE DIFFUSION MODERATOR, CAUSE ITS REMOVAL, OR OTHERWISE DAMAGE THE IMPLANT. SHOULD DAMAGE OCCUR, DO NOT INSERT THE IMPLANT AS PRODUCT FUNCTION CAN BE IMPAIRED.**

Loading the Implanter

1. The implanter is packaged in the correct configuration for implant loading and insertion. Make sure the cannula is fully extended as shown, and the actuator is in its most forward position.

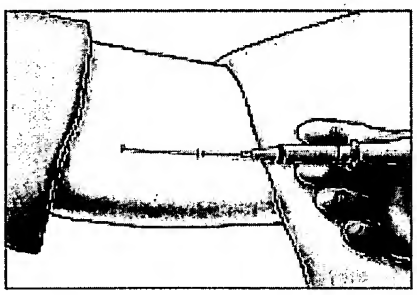


2. Using sterile forceps, slide the implant into the end of the cannula and push until it stops. When properly loaded, the implant should not protrude more than 1 mm past the bottom of the beveled edge.

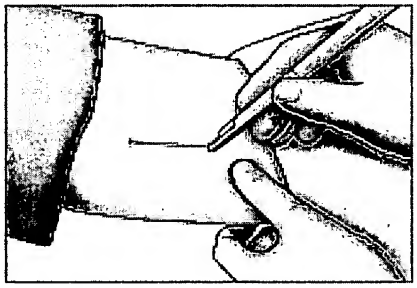


Inserting the Implant

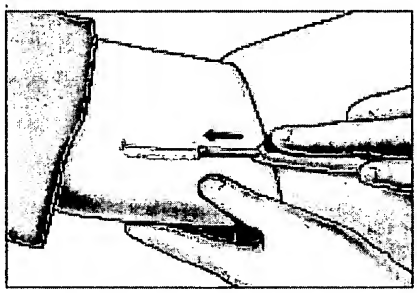
1. Using aseptic technique, cleanse the insertion site, then drape the patient's arm. After determining the absence of known allergies to the anesthetic agent, infiltrate the site with lidocaine. Advance the needle to infiltrate the intended 5 cm track for the implant insertion.



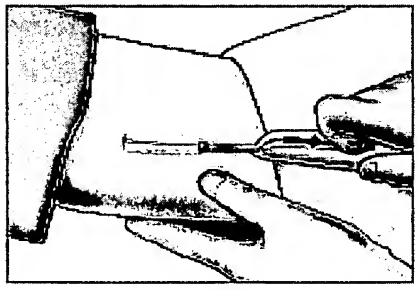
2. Determine that anesthesia is adequate. Make an incision of approximately 5 mm with the scalpel, just through the dermis.



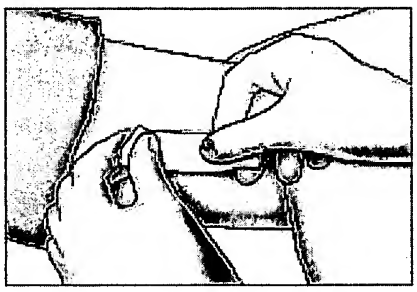
3. Grasp the handle of the implanter and extend the index finger to rest on the back of the actuator as shown. Insert the cannula tip into the incision with the bevel up and advance it subcutaneously along the intended track. To ensure subcutaneous placement, the Viadur® implanter should visibly raise the skin at all times during insertion. The implanter should not enter muscle tissue, but be well within the subcutaneous space. Advance the implanter to the depth indicator on the cannula, which indicates the recommended insertion length.



4. Holding the implanter handle in position, use the index finger to slide the actuator slowly back until it stops. (This retracts the actuator cannula into the handle, leaving the implant beneath the skin.). Do not pull back on the implanter handle while sliding the actuator back, as this may lead to incorrect positioning of the implant and subsequent extrusion. Withdraw the implanter from the incision. Release of the implant can be checked by palpation. It is important to keep the implanter steady and not to push the implant into the tissue. After placement, sterile gauze may be used to apply pressure briefly to the insertion site to ensure hemostasis.



5. Cleanse the insertion area. Press the edges of the incision together, and tightly close the incision with one or two surgical closure strips. Cover with an adhesive bandage. Observe the patient for a few minutes for signs of bleeding from the incision before he is discharged. Instruct the patient to keep the area clean and dry for 24 hours, and to avoid heavy lifting and strenuous physical activity for 48 hours. The surgical closure strip can be removed as soon as the incision has healed, ie, normally in 3 days.

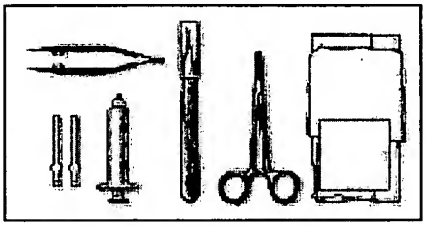


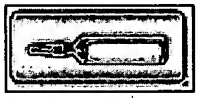
REMOVAL PROCEDURE

Viadur® must be removed following 12 months of therapy.

The position of the patient and the sterile technique are the same as for insertion.

To remove Viadur® use the Viadur® Kit or the following sterile items:



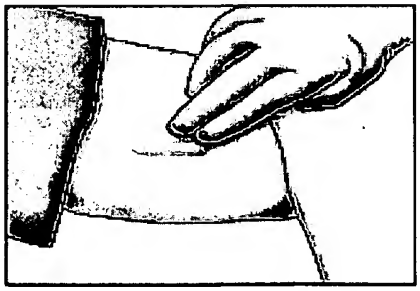


1 scalpel
1 forceps
1 syringe
1 package povidone-iodine swabs
1 package wound closure strips
1-22 Ga x 1.5" needle
1-25 Ga x 1.5" needle
1 sealed container of lidocaine HCl USP 2%, 10 mL
6 gauze sponges
2 alcohol prep swabs
1 package skin protectant
1 bandage
1 fenestrated drape
1 marking pen
1 ruler
1 mosquito clamp

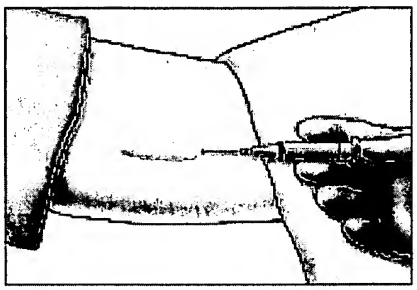
Preparing the Site

1. Inspect the site, palpating the location of the implant. Mark the position of the implant with marking pen. Cleanse with povidone-iodine swab. Drape the area with a fenestrated drape.

   Suggestion:
   If unable to locate by palpation, radiological imaging may be helpful.

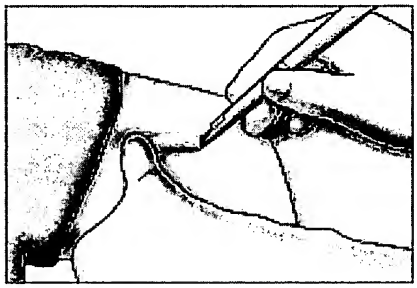


2. After determining the absence of known allergies to the anesthetic agent, apply a small amount of local anesthetic under the end of the implant nearest the original incision site. Then advance the needle to infiltrate the tissue along the track.

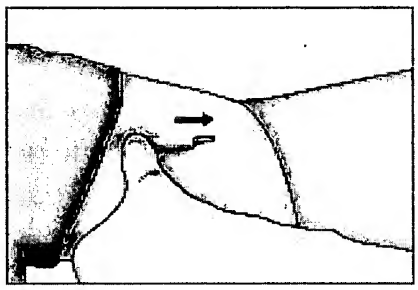


Removing the Implant

1. Determine that anesthesia is adequate. Apply pressure to one end of the implant to elevate the other end. Make an incision of approximately 5 mm at the elevated end of the implant. Do not make a large incision.



Continue to apply pressure to the end of the implant to encourage expulsion. Push the implant gently towards the incision with the fingers. When the tip is visible or near the incision, grasp it with a clamp and remove.



2. If necessary, cut through any fibrous encapsulation with the scalpel to free the implant.

3. Properly dispose of removed implant immediately, before opening the vial containing the new implant.

If inserting a new Viadur®, return to section describing **INSERTION PROCEDURE**.

The new Viadur® implant may be placed through the same incision site. Alternatively, the contralateral arm may be used.

4. Cleanse insertion site area. Apply pressure to each end of the incision to close the wound. Apply one or two surgical closure strips to close the wound tightly, and cover with an adhesive bandage. Observe the patient for a few minutes for signs of bleeding from the incision before he is discharged. Instruct the patient to keep the area clean and dry for 24 hours, and to avoid strenuous physical activity for 48 hours.

HOW SUPPLIED

Viadur® is supplied in a box containing 2 inner package trays. One tray contains a sterile Viadur® implant in a sealed vial, a sterile Viadur® implanter and a sealed container of lidocaine HCl USP 2%, 10 mL. The other tray constitutes a sterile Viadur® Kit, which includes: 1 scalpel, 1 forceps, 1 syringe, povidone-iodine swabs, 1 package wound closure strips, 1-22 Ga x 1.5" needle, 1-25 Ga x 1.5" needle, 6 gauze sponges, 2 alcohol prep swabs, 1 package skin protectant, 1 bandage, 1 fenestrated drape, 1 marking pen, 1 ruler, and 1 mosquito clamp. A physician insert, patient information, and insertion and removal instructions are also provided in the box.

(**NDC** 0026-9711-01)

Rx Only.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

For more information call 1-800-288-8371 or visit www.VIADUR.com.

REFERENCES

1. Sennello LT et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci* 1986; 75(2):158-160.
2. MacLeod TL et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987; 48(3):500-502.

™

An ALZA DUROS® Technology Product

Bayer HealthCare

Manufactured by:
ALZA Corporation
Mountain View, CA 94043 U.S.A.

Distributed by:
Bayer Pharmaceuticals Corporation
400 Morgan Lane, West Haven, CT 06516 USA

Viadur® and DUROS® are registered trademarks of ALZA Corporation under license to Bayer Pharmaceuticals Corporation. For further information about the product contact Bayer Pharmaceuticals Corporation.

Patient Information About:
Viadur®
(leuprolide acetate implant)

Important Information for Patients Using Viadur® for the treatment of symptoms of advanced prostate cancer.

Please read this information before you start using Viadur®. Each time another Viadur® is inserted, check the patient information leaflet for any new information. Remember, this information does not take the place of your doctor's instructions. Ask your doctor or pharmacist if you have questions or want more information about Viadur®.

What is Viadur®?

Viadur® is a drug-delivery system that contains the drug leuprolide and is placed under the skin. It looks like a small, thin metal tube. After it is placed under the skin, Viadur® delivers leuprolide to your body continuously for 12 months.

How does Viadur® work?

Leuprolide, the active medication in Viadur®, works by reducing the testosterone produced by the testicles. This lowers the amount of testosterone in the body. Testosterone appears to be needed by prostate cancer cells. Usually prostate cancer shrinks or stops growing when the body's supply of testosterone is lowered.

By lowering the amount of testosterone in the body, Viadur® may help relieve the pain, urinary problems, and other symptoms of prostate cancer. However, Viadur® is not a cure for prostate cancer. Once Viadur® is removed by your doctor, your body will start producing testosterone again.

How is Viadur® given?

Viadur® will be placed under the skin of your upper, inner arm. The doctor will numb your arm, make a small incision, and then place Viadur® under the skin. The incision will be closed with special surgical tape and covered with a bandage. You should keep the bandage in place for a few days until the incision heals.

After 12 months, Viadur® must be removed and may be replaced with a new Viadur® by your doctor.

What should I avoid while Viadur® is inserted?

After Viadur® is inserted, keep the site clean and dry for 24 hours. Do not bathe or swim for 24 hours. Avoid heavy lifting and physical activity for 48 hours. Avoid bumping the site for a few days. After the cut has healed, you should be able to go back to your normal activities.

What should I know about using Viadur®?

- If you notice unusual bleeding, redness or pain at the insertion site, contact your doctor.
- In the first few weeks of treatment, if you experience increased pain throughout your body, weakness, or numbness, contact your doctor.
- X-rays and MRI do not affect Viadur®.
- Viadur® is seen on X-rays. Slight image distortion around Viadur® may occur during MRI procedures.
- Viadur® must be removed and may be replaced after 12 months.

Who should NOT use Viadur®?

Do not use Viadur® if you are allergic to the drug leuprolide.

Do not use Viadur® if you are a woman. Viadur® is not approved for use by women of any age. Furthermore, use of Viadur® in a woman who is or may become pregnant may cause harm to the baby. You may lose your baby through a miscarriage if the drug is used while you are pregnant.

Viadur® was not studied in children and should not be used in children.

What are the most common side effects of Viadur®?

The most common side effects related to Viadur® were hot flashes, lack of energy, depression, sweating, headache, bruising, and breast enlargement.

Prostate cancer-related symptoms may become worse during the first few weeks of treatment.

Like other similar treatment options, Viadur® may cause impotence.

There may be some pain and discomfort during and after Viadur® insertion and removal. Bruising may occur. Reactions, such as itching and redness, are usually mild and heal without treatment within two weeks. If they do not heal, contact your doctor.

There is a chance that your bones may become thinner if you use this type of drug for long periods of time. Ask your doctor if this is a risk for you.

This list is not a complete list of all the possible side effects. If you need more information, or are worried about these or other side effects, talk to your doctor or pharmacist.

What tests will my doctor perform during my treatment with Viadur®?

Your doctor may measure blood levels of testosterone and prostate-specific antigen (PSA) during your treatment with Viadur®.

Can I take Viadur® with other medications?

Tell your doctor or pharmacist about any medicines that you are taking, including Viadur®, prescription, non-prescription, and herbal remedies. Do not start taking a new medicine before checking with your doctor or pharmacist.

For more information on Viadur®, talk to your doctor or pharmacist, call 1-800-288-8371 between 8:30 AM and 5 PM Eastern Standard Time, or visit www.VIADUR.com on the Internet.

An ALZA DUROS® Technology Product

Bayer HealthCare

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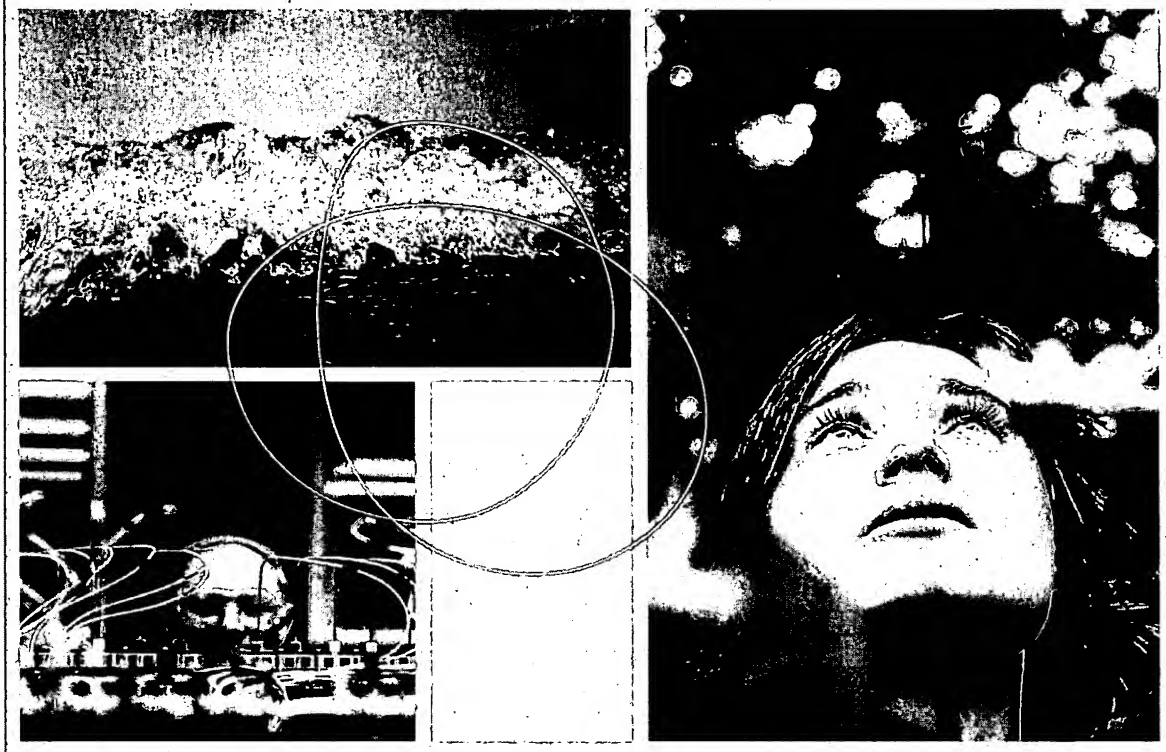
FMC BioPolymer
THE SCIENCE OF FORMULATION

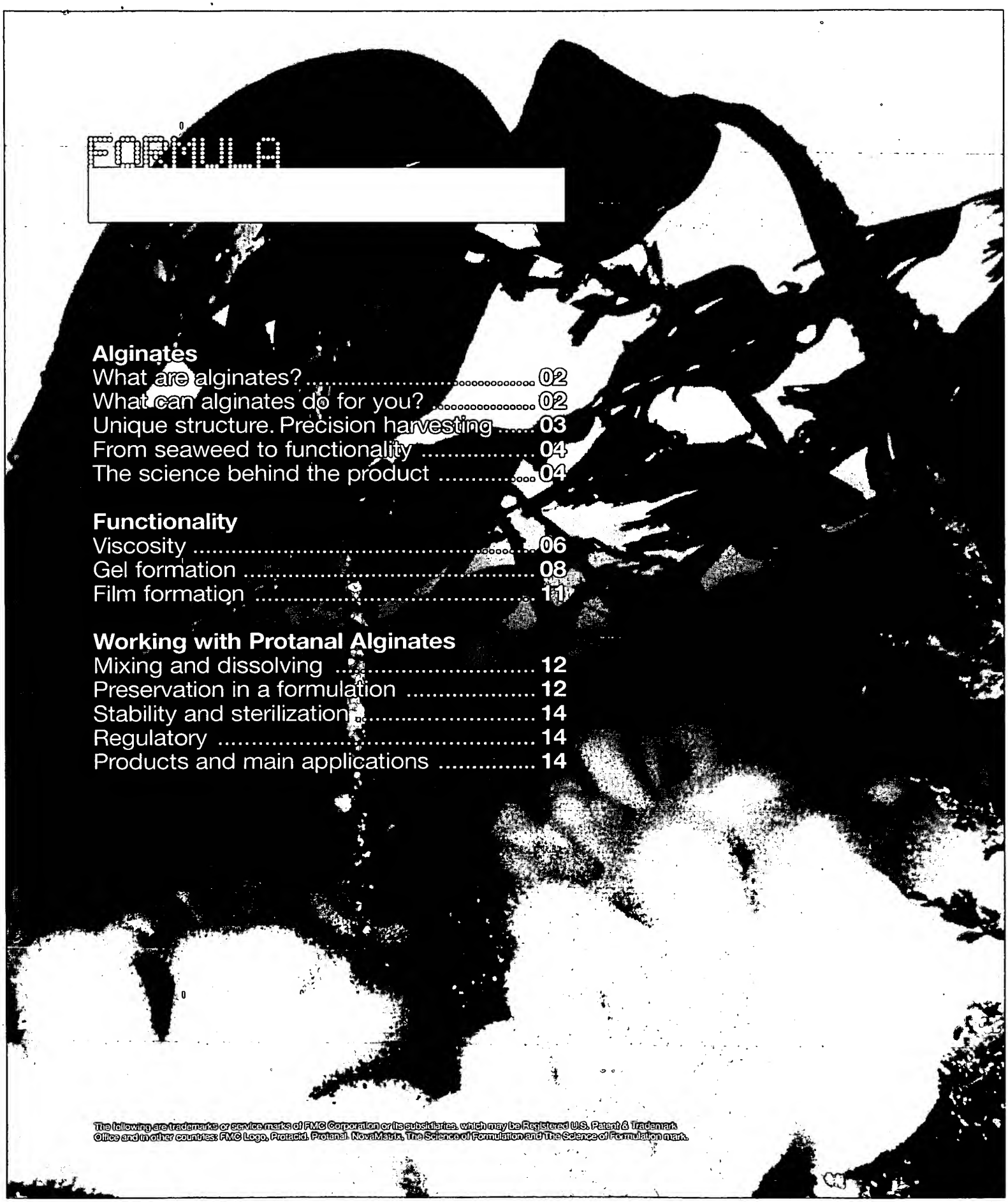
FMC

A WORLD OF POSSIBILITIES FOR YOUR FORMULATIONS



Protanal, Protacid, Protanal Ester

SOLUTIONS



FORMULA

FMC BioPolymer
THE SCIENCE OF FORMULATION

ALGINATES

A world of possibilities
lies just below the surface.

For over 60 years, we have built partnerships. We have pioneered new thinking. And we have created solutions. We look back on this legacy with pride, but we must also continue to look ahead. Now we're exploring a new generation of possibilities for an established technology, giving researchers and formulators another problem-solving toolset to enhance the patient experience and improve healthcare.

Alginates personify the possibility of science. Extracted from brown seaweeds that grow rich and plentiful in consistently cold, clear waters, alginates have already proven themselves in numerous applications.

But as much as we've learned about alginates, we know that we've penetrated only the first layers of discovery. Applying our scientific expertise and our passion for leaving no problem unsolved, we seek to develop the full potential of this material, working alongside our partners and customers to turn ideas into practical, profitable reality.

We challenge you to think beyond what's been done and imagine what could be. We invite you to join us as we redefine the potential of one of nature's building blocks. Together, we can push new boundaries and discover what's really possible for alginates and the human condition.

What are alginates?

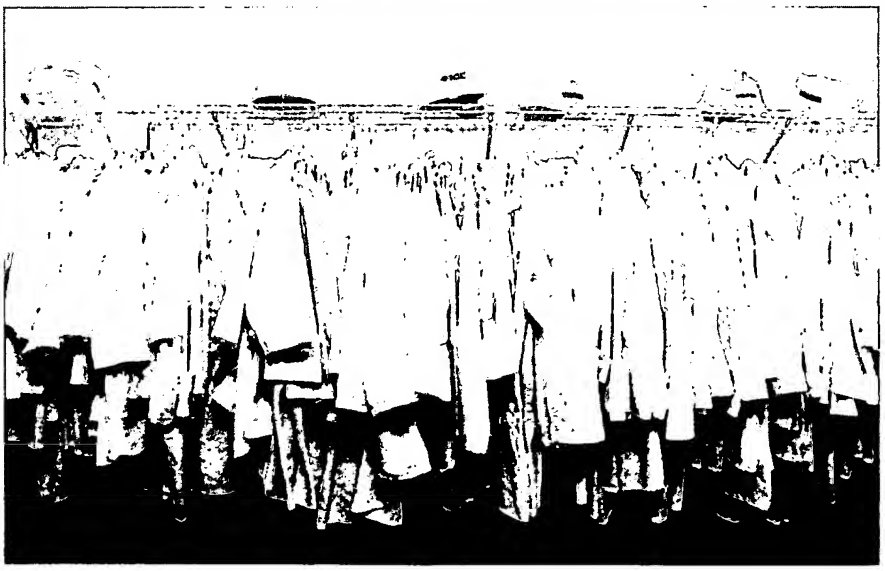
Alginates are hydrocolloids, water-soluble biopolymers extracted from brown seaweed. They were first researched in the late 19th century by British chemist E.C. Stanford, although it was another 50 years before they were produced commercially. Since that time, scientists have discovered much about this versatile material. Not just new knowledge of its multiple properties (such as gelling, film-forming, thickening and stabilizing characteristics)—but also how to adjust harvesting and processing methods to enhance those properties.

While alginates are natural products derived from a natural origin, FMC BioPolymer has refined its harvesting and processing techniques for maximizing yield and ensuring batch-to-batch consistency.

What can alginates do for you?

As formulators who are familiar with alginates have already learned, this hydrocolloid has many attributes which naturally lend to a variety of applications. They possess unique, valuable functionality in esophageal anti-reflux suspensions and tablets, and have demonstrated promise in the area of controlled release medications. They also offer benefits as viscosifiers and disintegrants, and can be customized so that their gel-forming characteristics facilitate matrix and structural building properties. Alginates' wide range of gel strengths have made them a mainstay of the dental impression and denture adhesive markets for decades. And in the areas of wound care and dermatology, their ability to create films, foams and fibers offers a wide range of potential uses. Regardless of this history of success, we believe that the best is yet to come for alginates.

Regardless of this history of success, we believe that the best is yet to come for alginates.



Unique structure. Precision harvesting

The primary brown seaweed utilized by FMC BioPolymer for the extraction of alginates is *Laminaria hyperborea*, which is harvested off the west coast of Norway.

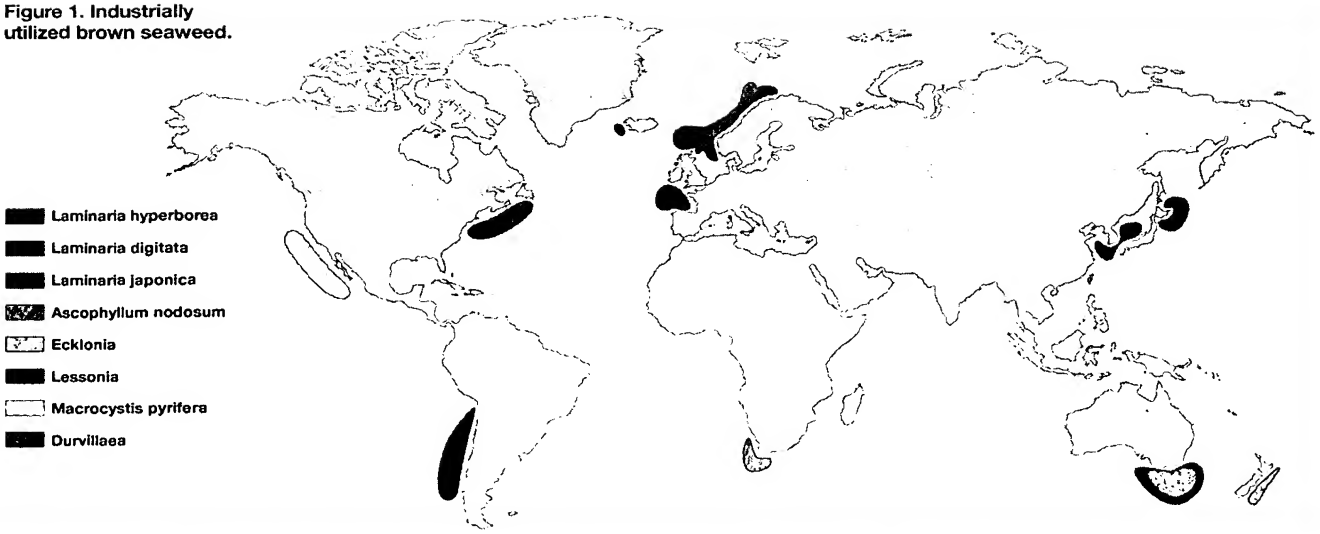
At these latitudes the waters are clear and clean, resulting in a healthy, sustainable, renewable crop which grows just below the surface. Water temperature also plays an important role, and the consistently cold water found in this region results in plants containing alginates with a molecular structure that accentuates their useful properties.

Using a proprietary process employing specially designed trawlers and mechanical harvesting equipment, FMC harvests seaweed in a way that sustains regrowth, in accordance with advice provided by the Norwegian Marine Research Institute and the Directorate of Fisheries. This responsible resource management solidifies our position as a long-term provider of a consistent, reliable supply of highly functional, cost-effective alginates to customers in the pharmaceutical and medical industries.

In order to supply alginates with different functionalities, FMC BioPolymer also utilizes other sources of brown seaweed, which are harvested off the Chilean coast **(figure 1)**.

At these latitudes the waters are clear and clean, resulting in a healthy, sustainable, renewable crop which grows just below the surface.

Figure 1. Industrially utilized brown seaweed.



From seaweed to functionality

Alginate occurs naturally in seaweed mainly in the form of calcium, magnesium and sodium salts. To transform seaweed into products like Protanal alginates and Protacid alginic acid, FMC has developed a process that extracts alginate while thoroughly removing all other biological and inorganic impurities **(figure 2)**. This stringently controlled process ensures that our alginates are of a consistently high quality.

Whether your needs call for excipient grade, active pharmaceutical or ultrapure grade alginates, you can be sure that FMC employs and adheres to the highest relevant standards to ensure purity and consistency.

We offer an array of over 100 alginate products—including alginic acid and its salts (sodium, triethanolamine, potassium, ammonium, magnesium, calcium) and varying grades of esterified alginate in the form of propylene glycol alginate—making us one of the world's largest and broadest suppliers of alginate-based materials.

What does this mean for you? It means that FMC's alginate products are among the most reliable in the industry. It means that you can introduce alginates into the formulation process with the highest degree of confidence. And it means that we're able to provide the versatility you need to ensure success in a wide range of formulations.

The science behind the product

Alginates are polysaccharides (carbohydrate polymers) with building blocks comprised of two uronate sugars, the salts of mannuronic and guluronic acid. When extracting alginates from harvested material, the uronic acids are converted into the salt forms mannuronate (M) and guluronate (G) through a neutralization step **(figure 3)**.

Alginate is a block copolymer composed of longer homopolymeric regions of M or G, potentially separated by regions of alternating structure (MG) **(figure 4)**. The proportion, distribution and length of these blocks determine the chemical and physical properties of the alginate molecules. While G-blocks provide gel-forming capacity, MM and MG units provide flexibility to the uronic acid chains, with flexibility increasing in the order GG<MM<MG.

The chemical composition of alginate varies according to seaweed species and structure. FMC BioPolymer has the experience and expertise to select the appropriate seaweeds (or combinations of seaweeds), and process them in a way that assures consistency over a wide range of functionalities.

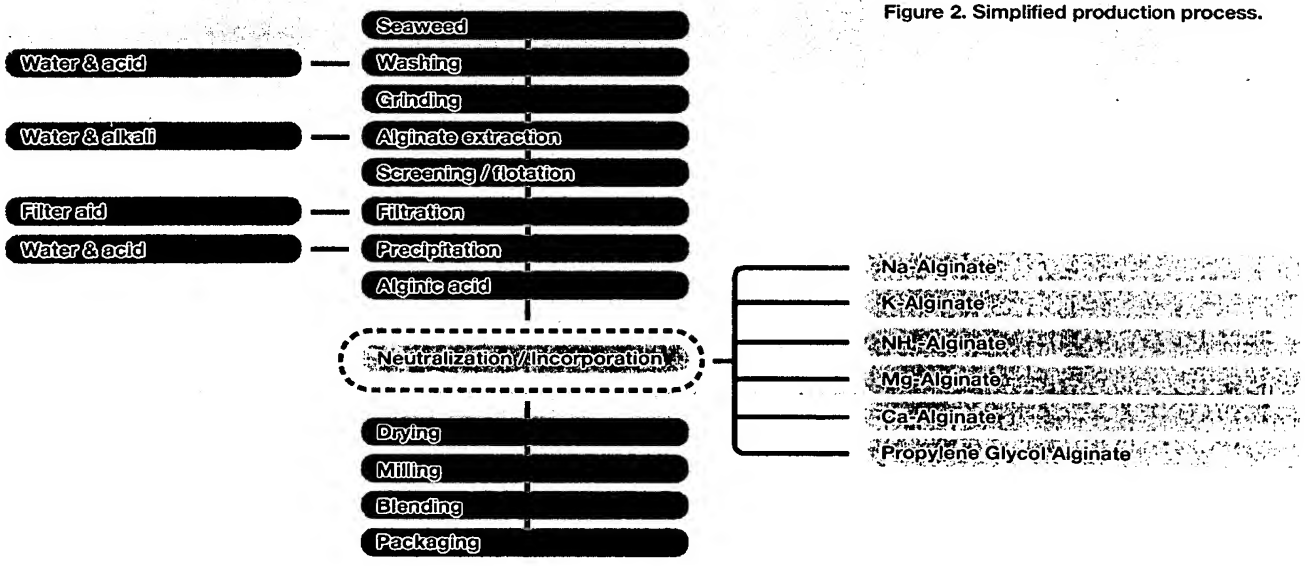


Figure 2. Simplified production process.

Figure 3. The monomers of alginate.

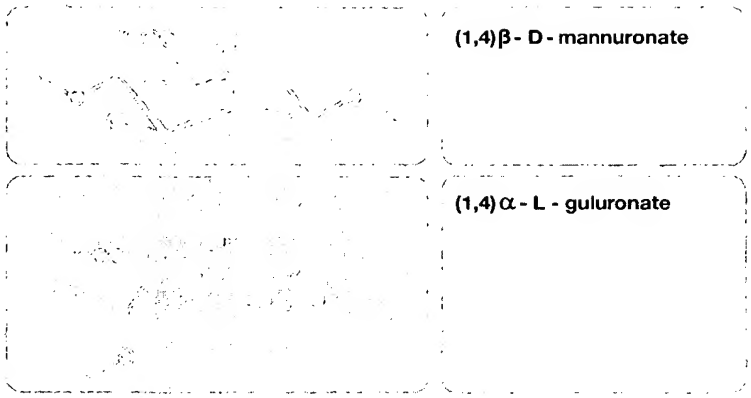
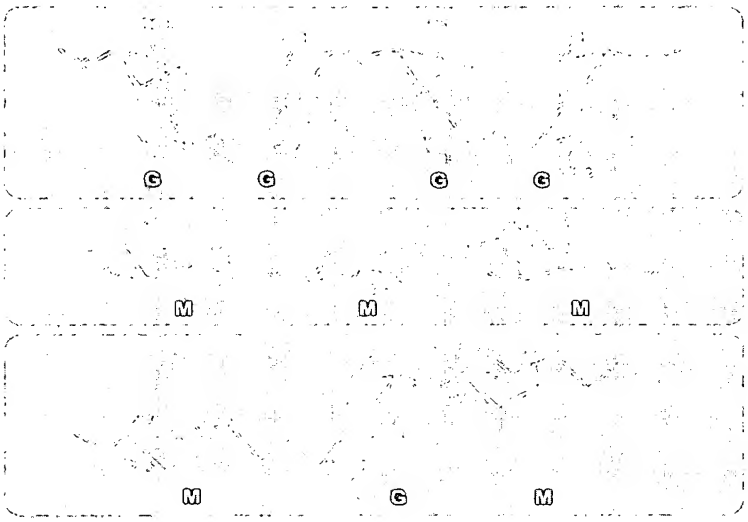


Figure 4. Alginate block types.



FUNCTIONALITY

Viscosity

Careful selection and management of our resources, highly developed harvesting techniques and stringent processing give us the ability to control alginate properties, such as gel strength, particle size and viscosity. You provide the target—we have the raw material and the technology to meet it.

Complete hydration of alginates is necessary to obtain full functionality of the polymer. The viscosity of an alginate solution depends on the alginate concentration and length of the alginate molecules, or the number of monomer units in the chains (i.e., average molecular weight), with longer chains resulting in higher viscosities at similar concentrations **(figure 5)**. Aqueous solutions of alginates have shear-thinning characteristics, meaning that viscosity decreases as the shear rate, or stirrer speed, increases **(figure 6)**.

This property is known as pseudoplasticity, or non-Newtonian flow. Temperature will influence viscosity as well, with increasing temperature resulting in decreased viscosity **(figure 7)**.

Standard grades of alginate form gels in acidic conditions. The pK_a values for mannuronic and guluronic acid are 3.38 and 3.65, respectively. However, propylene glycol alginate (PGA) is soluble in acid. PGA is produced by reacting the free carboxylic group of the alginic acid with propylene oxide **(figure 8)**.

Figure 5. Viscosity as a function of concentration of Protanal alginate.

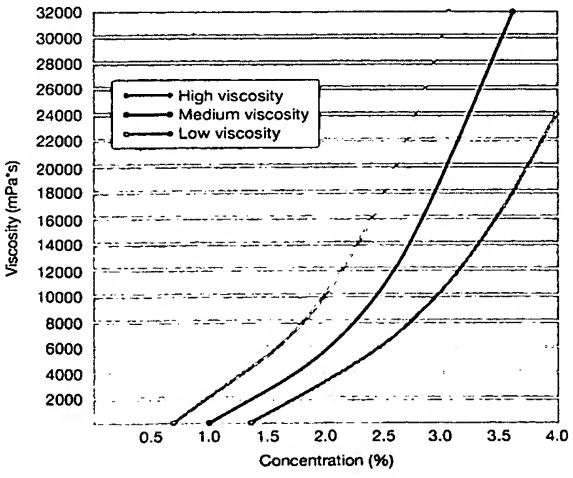


Figure 6. Viscosity as a function of shear rate.

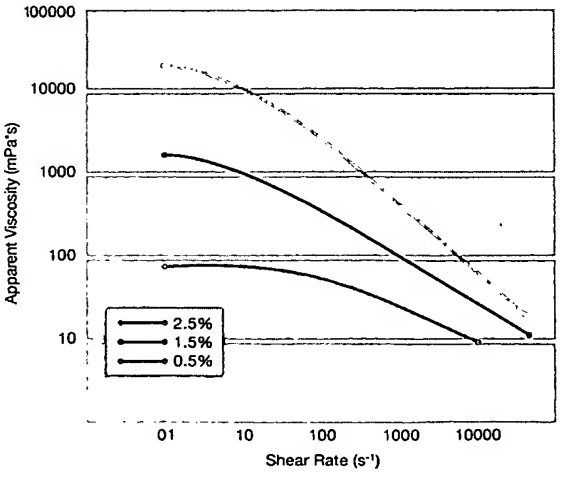


Figure 7. Viscosity of three 1% Protanal alginate solutions at different temperatures.

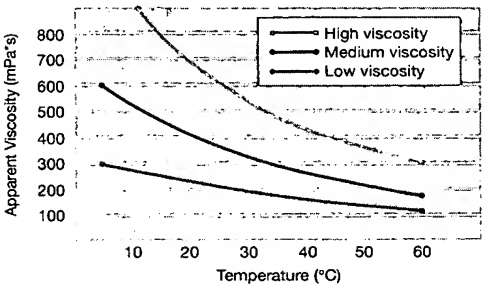


Figure 8. Propylene glycol alginate: Alginic acid chain with some acid residues esterified (R indicates ester group, H indicates acid group).

Gel formation

Gel formation is another area in which alginates have shown great promise. An alginate's ability to form a gel is determined by the proportion and length of G-blocks in its molecular structure, a position of strength for FMC's alginates due to several factors **(table 1)**. First, we use *Laminaria hyperborea*, which has one of the highest G-block contents of any species. Because the stems of *Laminaria hyperborea* possess the highest concentrations of guluronate monomers we process these stems separately, resulting in alginates with superior gel-forming capabilities. Second, our choice of harvesting location—cold, rough waters—facilitates higher G-block content. And finally, proprietary processing refinements enable us to extract alginates that form stronger gelling networks.

To fully appreciate the potential of alginate's gel-forming properties, it helps to understand the chemistry behind gel formation. Regions of guluronate monomers, or G-blocks, in one alginate molecule can be linked to a similar region in another alginate molecule by means of calcium ions or other multivalent cations **(figure 9)**. The divalent calcium cation, Ca^{2+}, fits into the guluronate block structure like eggs in an egg box **(figure 10)**. This binds the alginate polymers together by forming junction zones, resulting in gelation of the solution.

Table 1. Typical M- and G-block profiles for different seaweeds as measured by nuclear magnetic resonance spectroscopy (NMR).

	Type of seaweed	%MM	%MG & GM	%GG
Available from FMC	Laminaria hyperborea (stem)	17	26	57
	Laminaria hyperborea (leaf)	36	38	26
	Lessonia nigrescens	40	38	22
	Lessonia trabeculata	25	26	49
	Durvillaea antarctica	56	26	18
	Laminaria digitata	43	32	25
	Ecklonia maxima	38	24	28
	Macrocystis pyrifera	38	46	16
	Ascophyllum nodosum	44	40	16
	Laminaria japonica	48	36	16

Once formed, an alginate gel may be considered part solid and part solution. Water and other molecules are physically trapped within the alginate matrix by capillary forces, yet remain free to migrate by diffusion, depending on size. This property makes alginate gels ideal for multiple applications, including cell immobilization and/or encapsulation. Another area where this property plays a role is in wound treatment where the gel network is rehydrated through the absorption of exudates from wounds into alginate wound dressings. Also, in the treatment of anti-reflux diseases, alginates react *in situ* with acid and calcium carbonate, creating a protective, floating gel raft, due to the trapped bubbles of carbon dioxide.

Another valuable property of alginates is that they are soluble in cold water and do not need a heating and cooling cycle to form gels, as is the case with most other gelling biopolymers. By selecting alginate grades and adjusting formulations, alginate gels can be developed into a range of structure types, from firm and brittle to soft and pliable.

There are three main components in a typical alginate gelling system—alginate, calcium salt and sequestrant. Alginate type and counter-ion, calcium source and the sequestering agent control the gelling system structure and the rate at which the gel forms. Hydration and uniform distribution of the alginate are essential to optimize gel formation. The grade of alginate, calcium source and sequestering agents must be matched with the process and overall formulation to develop the final product **(figure 11)**. This is an area where our 60 years of experience yields huge dividends for our customers.

Figure 9. Calcium binding site in G-blocks.

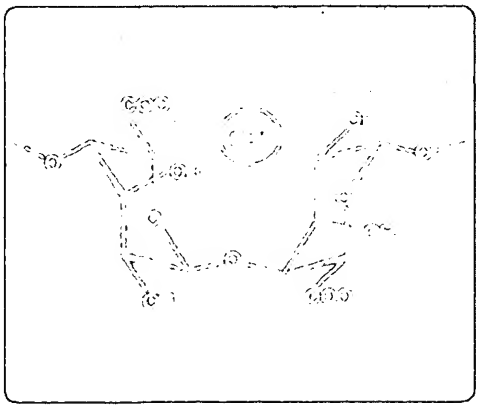


Figure 10. "Egg box" model for alginate gel formation.

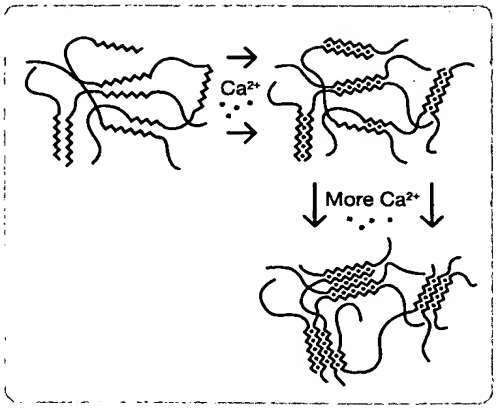
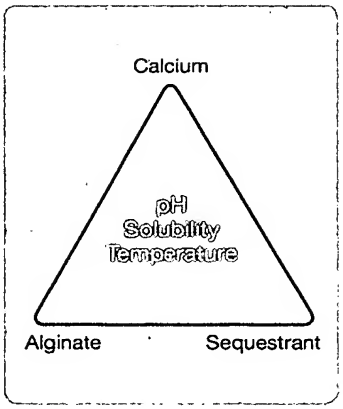


Figure 11. Factors influencing gel formation and properties.



While alginates naturally lend themselves to multiple gelling methods, the two most frequently used are diffusion setting and internal setting.

In a diffusion setting system at neutral pH, an alginate solution, or a mixture containing alginate, is gelled by being dipped into, or sprayed with, a calcium salt solution (calcium chloride is the most commonly used). The calcium ions diffuse into the solution and react with the alginate molecules, forming a calcium alginate gel. This process is especially suitable for relatively thin or small dimension materials, or when trying to provide a thin coating on a product surface. The rate of diffusion can be increased by raising the concentration of calcium in the setting bath or spray and by using a strongly calcium-reactive alginate, such as an alginate with a high proportion of G-blocks.

One example of using diffusion setting is in manufacturing calcium alginate fibers for wound dressings. In this case, alginate solution is extruded into a calcium bath through fine nozzles and the fibers gel by calcium diffusion into the fine threads. This principle is also used when encapsulating cells or materials in alginate beads.

The diffusion setting system can also be triggered by lowering pH. To accomplish this, a calcium salt that is insoluble at neutral pH is mixed with the alginate. When the acid comes into contact with the surface of this mass, the calcium salt is solubilized. The solubilized calcium will then react with the alginate, triggering the gelation process. One example of this application is anti-reflux medicines, where alginate forms a protective raft in the stomach.

In an internal setting process, calcium is released within the product under controlled conditions. This method employs the combination of alginate, a slowly soluble calcium salt and a suitable calcium sequestrant, such as a phosphate or citrate. A sequestrant is needed to bind free calcium and prevent pregelation of the alginate during the time the product is mixed (prior to being cast into the desired shape). The shorter the mixing time, the lower the level of sequestrant needed.

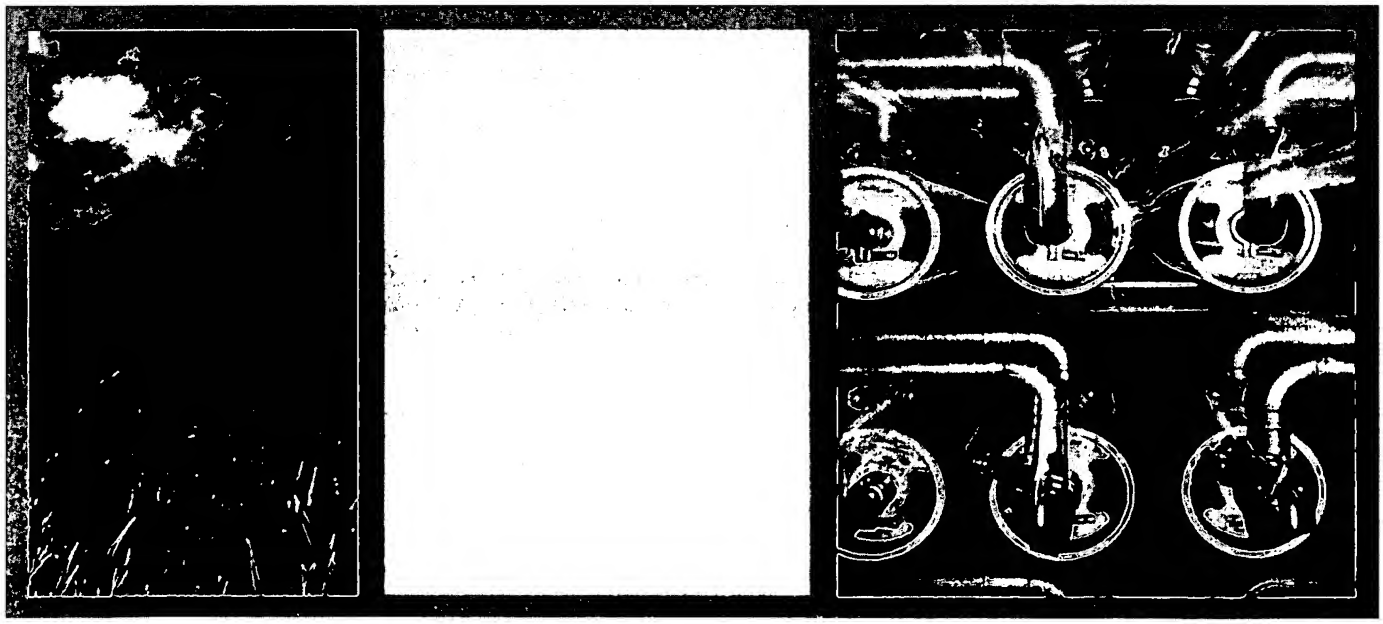
The internal setting method may be performed at neutral or acidic pH and acidity may be achieved through the addition of an acidifier, which will accelerate the solubility of the calcium salts. This method is commonly used for dental impression materials.

Film formation

Another attribute of alginates which presents exciting possibilities is its film-forming capability. While several biopolymers can be used for film formation, alginate's inherent properties give it some distinct advantages. Films formed using alginates in combination with a plasticizer are generally strong and flexible, and also provide a strong oxygen barrier. Alginate films also offer excellent transparency and can be either soluble or insoluble. Soluble films of sodium alginate are made by casting and drying, while insoluble or gelled alginate films are produced by applying a layer of alginate solution followed by cross-linking with calcium salt and then drying.

We see several possibilities to leverage the inherent flexibility and other unique properties of alginates. For example, alginate's film-forming capabilities could provide potential new platforms for the innovative drug delivery systems of the future.

Alginate's film-forming capabilities could provide potential new platforms for the innovative drug delivery systems of the future.



FMC BioPolymer
THE SCIENCE OF FORMULATION

WORKING WITH PROTANAL ALGINATES

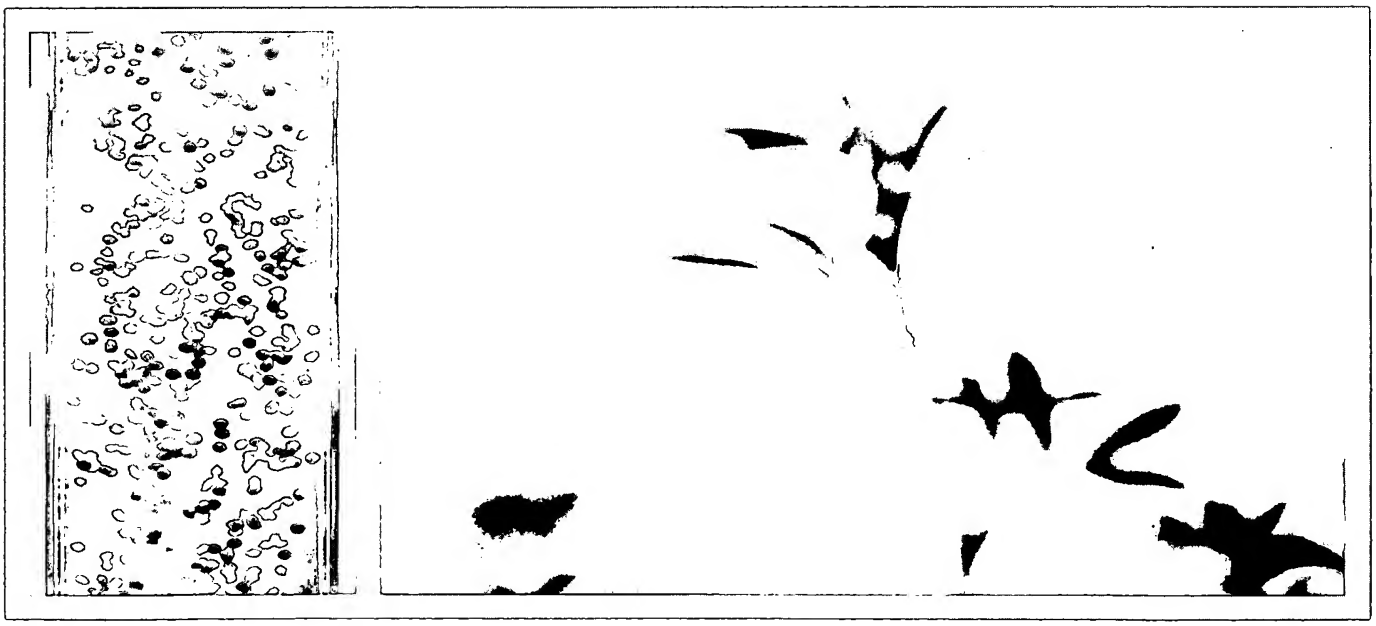
When working with alginates, it's important to follow a few simple guidelines

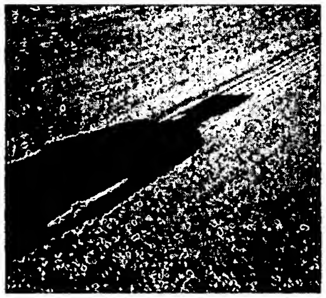
Mixing and dissolving

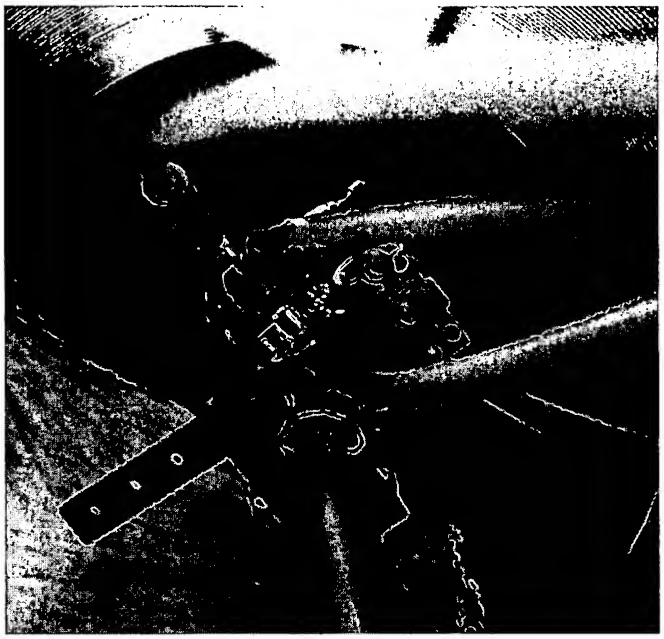
During the dissolving process, it is crucial that the water be vigorously stirred while powder is being added. Protanal alginates should be introduced slowly into the vortex created by the water to avoid lumping and stirred until complete hydration occurs (5 to 20 minutes, depending on the grade of Protanal alginate and equipment used). Premixing with another powder or in a liquid that does not dissolve alginate (such as alcohol, PEG or oil) will enhance dispersion and subsequent dissolution.

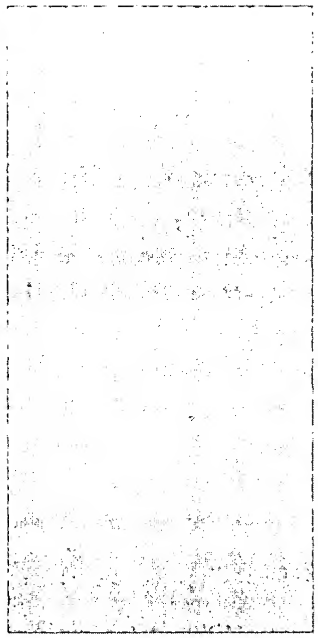
Preservation in a formulation

Although naturally derived alginates are less susceptible to microbial attack than many other carbohydrates, preservatives are recommended for use in systems with high moisture or suspensions. When on the lookout for the presence of microbial growth, one clear indicator is a reduction in viscosity. Preservatives like sorbic acid, potassium sorbate, benzoic acid, sodium benzoate or esters of hydroxybenzoic acid can all be safely employed when trying to prevent growth. The amount required will depend on the type of preservative, the composition of the product and the storage conditions.









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Stability and sterilization

Time, temperature and humidity influence the stability of alginate systems. The stability of Protanal alginates and Protacid alginic acid is well established and has been documented through FMC's alginate stability program. FMC has developed packaging and distribution techniques that help ensure stability, allowing customers to take delivery of product shipments with a high degree of confidence. FMC has also optimized product logistics to ensure reliable delivery and maintain product quality and integrity during shipment. Once customers receive Protanal alginate shipments, it is recommended that they be stored cool (8-15° C) and dry, while Protacid alginic acid, which is less stable than sodium and potassium alginate, should be stored cold (less than 5° C) and dry.

As with most carbohydrates, alginates are susceptible to hydrolysis or degradation in acid and alkali, especially when exposed to high temperatures over extended periods. To limit this possibility, apply high heat only when needed and for as short a time as possible. If use of high heat is undesirable, sterilization can also be achieved through filtration via an appropriate submicron filter.

Sterile alginates have achieved great success in encapsulation of living cells that release biologically active substances to treat conditions such as diabetes and brain tumors. Sterile and ultrapure alginates can be obtained through our NovaMatrix business unit.

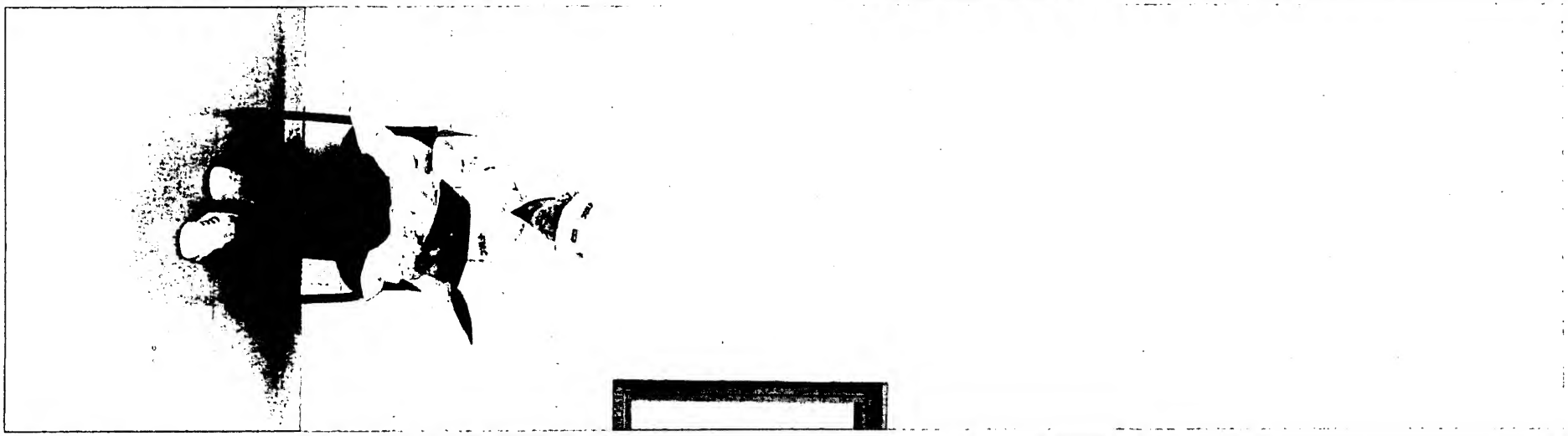
Regulatory

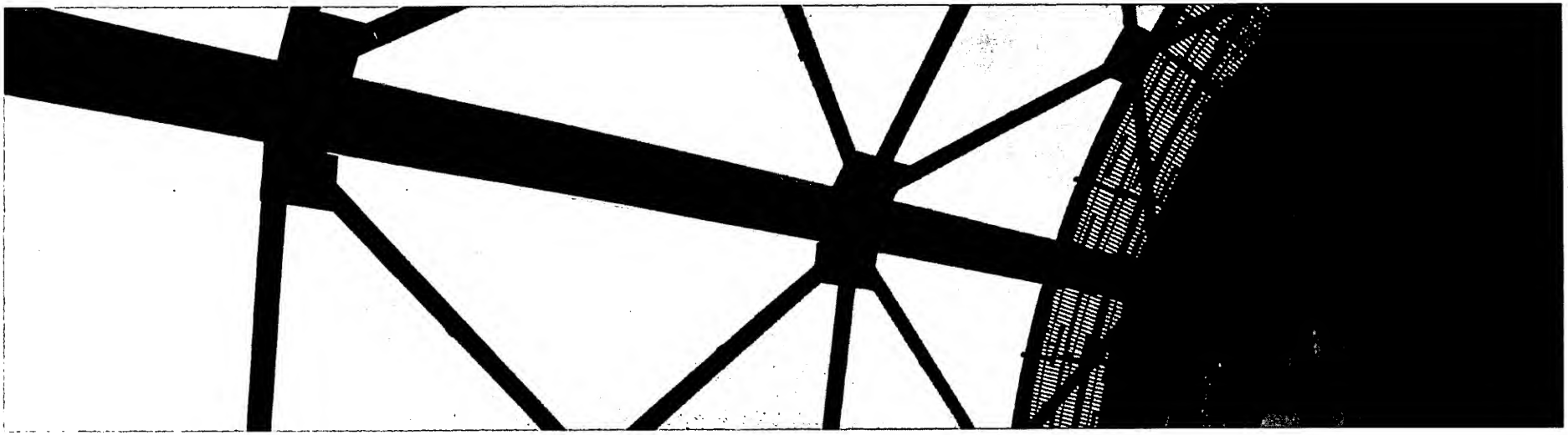
Protacid alginic acid and Protanal sodium alginate meet the requirements of the monographs in the National Formulary (NF) and European Pharmacopoeia (Ph.Eur.). Protanal Ester propylene glycol alginate meets the requirements of the monograph in the NF. A Type IV Drug Master File is on file with the U.S. Food and Drug Administration for Protanal sodium alginate. No compendial monographs currently exist for magnesium alginate, potassium alginate or triethanolamine alginate.

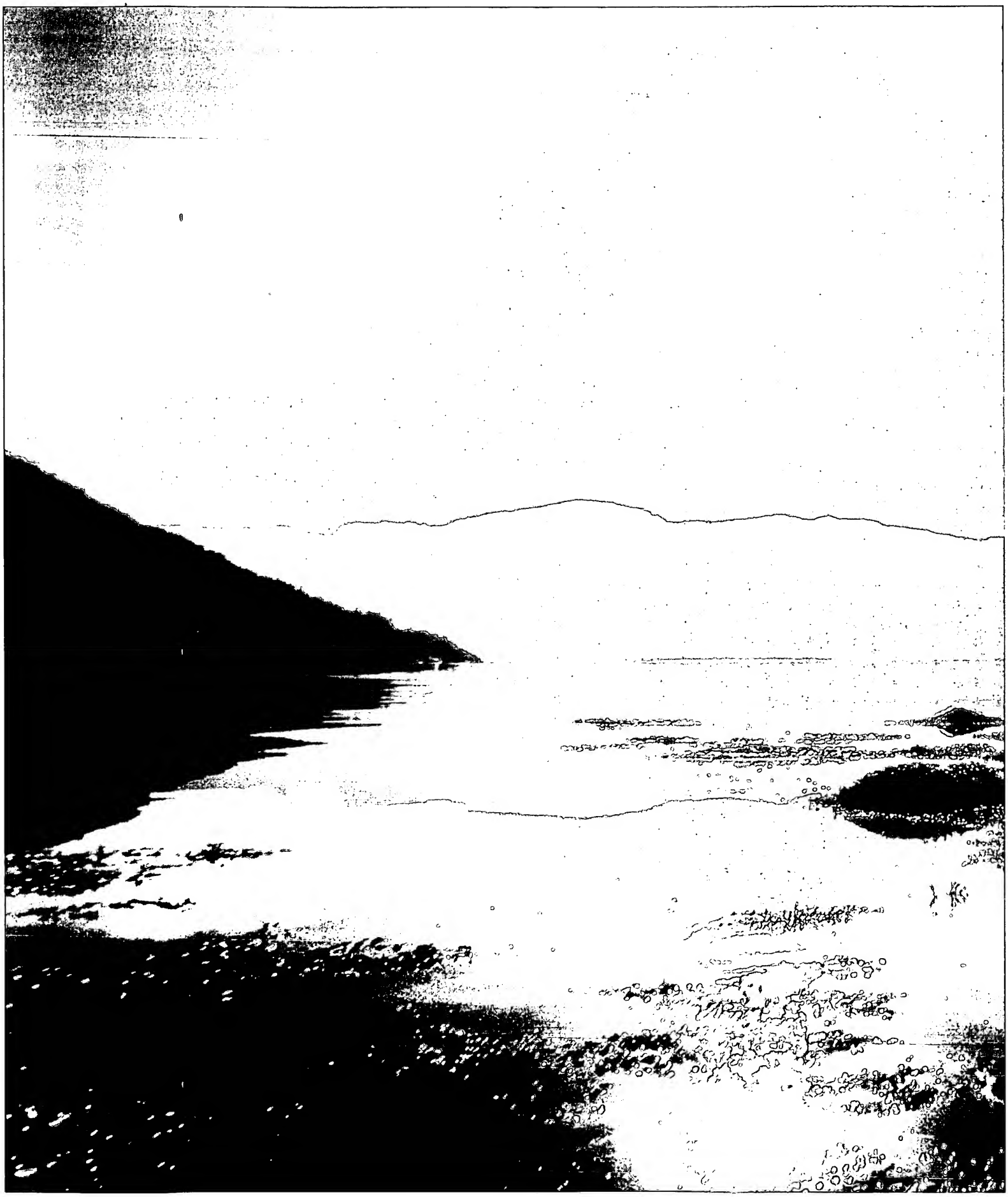
Nature, Humans, Science photography shot on location by: Jake Chessum. Alex Williams/JDK Photostudio.

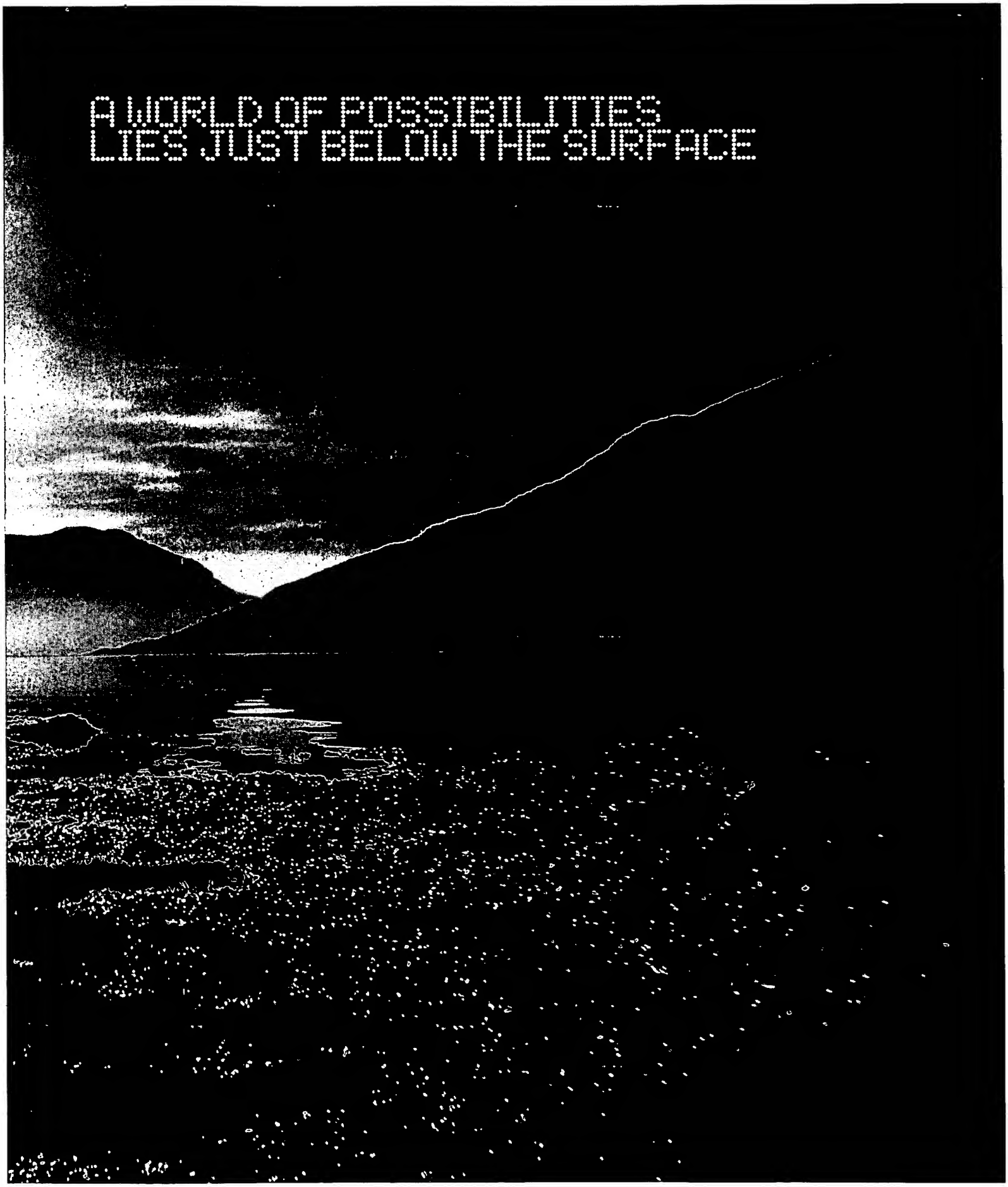
Products and main applications

Type of alginate	Brand name	Main applications
Alginic acid	Protacid	Anti-reflux tablets, natural disintegrant
Sodium alginate	Protanal	Anti-reflux suspensions, controlled release tablets, wound dressings, dental impression material, denture fixatives, viscosifier, encapsulation, films, foams
Magnesium alginate	Protanal	Anti-reflux suspensions for infants
Potassium alginate	Protanal	Dental impression material
Triethanolamine alginate	Protanal	Dental impression material
Propylene glycol alginate	Protanal Ester	Suspending agent/stabilizer, plastisizer, binder, emulsifier





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The products, processes and uses thereof described herein are covered by one or more patent applications or patents.

Warranty:
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Technical Service:
The information contained in this bulletin is intended to be general in nature. Techniques and data pertaining to specific uses for FMC BioPolymer products and new developments will be published periodically in the form of supplemental application bulletins. Our technical staff is ready to offer assistance in the use of FMC BioPolymer products.

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